AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS COMMITTEE

March 24, 2004
12:45 p.m.

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1. Opening Remarks……Chair
2. Approval of December 10, 2003 Meeting Minutes
3. Pharmacy Program Update……Alabama Medicaid
4. Oral Presentations by Manufacturers/Manufacturers Representatives
5. Pharmacotherapy Reviews
    - Serotonin 5-HT1 Receptor Agonists/Triptans
    - Estrogens
        - Single Entity Products
        - Combination Products
    - Intranasal Corticosteroids
    - Respiratory Classes
        - Antimuscarinics/Antispasmodics
        - Inhaled Corticosteroids
        - Respiratory Smooth Muscle Relaxants
            i. Single Entity Products
            ii. Combination Products
        - Sympathomimetic Agents
            i. Single Entity Products
            ii. Combination Products
        - Unclassified Therapeutic Agents
            i. Leukotriene Modifiers
            ii. Mast Cell Stabilizers
    - Cardiac Classes
        - Antiarrhythmic Agents
        - Cardiotonic Agents
        - Nitrates and Nitrites
6. New Business
7. Next Meeting Date
8. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
Pharmacotherapy Reviews

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
Miscellaneous Central Nervous System Agents, Triptans (AHFS Class 289200)
March 24, 2004

Overview

Serotonin 5-hydroxytryptamine (5-$HT_{1B/1D}$) agonists, commonly referred to as "triptans" are used to treat migraine and certain other headaches. Through activation of vascular 5-$HT_{1B/1D}$ receptor subtypes, these agents have three potential main mechanisms of action; cranial vasoconstriction, peripheral neuronal inhibition, and inhibition of transmission through second-order neurons of the trigeminocervical complex.[1]

Sumatriptan was the first triptan introduced in 1991. Currently there are seven triptans on the market (see Table 1). These agents differ slightly in their pharmacological and pharmacokinetic profiles relative to one another. Additionally, these agents are available in a variety of dosage forms including tablets, orally disintegrating tablets, subcutaneous injection and intranasal spray. This review encompasses all dosage forms and strengths.

Table 1. Current triptans and dosage forms available in the U.S.

Generic Name*	Brand Name Example(s)	Dosage Form
Almotriptan	Axert®	Oral tab
Eletriptan	Relpax®	Oral tab
Frovatriptan	Frova®	Oral tab
Naratriptan	Amerge®	Oral tab
Rizatriptan	Maxalt®	Oral, orally disintegrating tab
Sumatriptan	Imitrex®	Oral, S.C., intranasal
Zolmitriptan	Zomig®	Oral, orally disintegrating tab, intranasal

*No generic forms were available when this review was conducted

Current Treatment Guidelines

Triptans are recommended as first line therapy in patients with moderate to severe migraine with no contraindications for their use or after treatment failure with NSAIDs.[2,3]

Indications

Drugs for migraine are often classified by whether they are taken to prevent migraine attacks (prophylaxis) or to shorten (abort) an acute attack. All of the triptans available in the U.S. are approved by the FDA for acute treatment of a migraine attack in adults with or without aura. None of these agents are approved for prophylaxis of migraine or for hemiplegic or basilar migraine. Sumatriptan injection is the only triptan formulation approved for cluster headache.

Pharmacokinetics

Table 2 compares the triptan pharmacokinetic parameters. Notable differences occur with onset, half-life and bioavailability.

Table 2. Pharmacokinetic Parameters of Triptans in Healthy Volunteers and in Patients with Migraine[4]

Drug	Dose and route of administration	Onset (h)	T_{max} (h)	Bioavailability (%)	$t_{1/2}$ (h)	Plasma protein binding (%)
Almotriptan	12.5 mg PO	0.5-2	2.5	80	3.1	
	25 mg PO		2.7	69	3.6	
Eletriptan	20 mg PO	1	2	≈50	≈4	≈85
Frovatriptan	2.5 mg PO	2-3	3	29.6	25.7	≈15
	40 mg PO		5	17.5	29.7	
Naratriptan	2.5 mg PO	1-3	2	74	5.5	20
Rizatriptan	10 mg PO	0.5-2	1	40	2	14
Sumatriptan	6 mg SC	0.2	0.17	96	2	14 to 21
	100 mg PO	0.5-1	1.5	14	2	
	20 mg IN	0.25-0.3	1.5	15.8	1.8	
Zolmitriptan	2.5 mg PO	0.75	1.5	39	2.3/2.6*	25
	5 mg PO		1.5	46	3	
	5 mg IN	0.25	1-3	41	3	

*Value for men and women, respectively

The following bullet points summarize the effects of renal impairment on individual triptan therapy[5-12]:

- Sumatriptan is metabolized into an inactive metabolite. Little clinical effect is expected with renal impairment.
- Clearance of zolmitriptan is reduced by 25% in patients with severe renal impairment (Ccr approximately 5 to 25 mL/min); no significant change is observed in those with moderate renal impairment.
- Rizatriptan should be administered with caution in dialysis patients due to decreased rizatriptan clearance.
- Naratriptan is contraindicated in patients with severe renal impairment. For those with mild or moderate renal impairment the maximum daily dose should not exceed 2.5 mg.
- Clearance of almotriptan in patients with severe renal impairment is reduced, therefore the maximum daily dose should not exceed 12.5 mg.
- Less than 10% of frovatriptan is excreted in urine after an oral dose. It is unlikely that the clearance of frovatriptan is affected by renal impairment.
- No significant change in eletriptan clearance is observed in patients with mild, moderate or severe renal impairment. However, small transient dose related increase in blood pressure is more pronounced in patients with renal impairment.

The liver plays an important role in the presystemic clearance of several oral 5-HT_1 agonists. Accordingly, the bioavailability may be markedly increased in patients with liver disease. The following bullet points summarize the effects of hepatic impairment on individual triptan therapy:[5-12]

- Naratriptan is contraindicated in patients with severe hepatic impairment.
- Lower doses and monitoring of blood pressure are recommended specifically with sumatriptan, almotriptan, and zolmitriptan.
- Rizatriptan should be used with caution in patients with moderate hepatic impairment. Changes in hepatic clearance of rizatriptan in patients with mild hepatic insufficiency are similar to placebo.
- No dose adjustment is necessary with eletriptan in patients with mild to moderate hepatic impairment. However, the use of eletriptan in patients with severe hepatic impairment is not recommended.
- No recommendations are provided for frovatriptan in patients with hepatic impairment. In patients with mild to moderate hepatic impairment, the AUC has been reported to be twice as high when compared to young, healthy patients, but within the range found among normal healthy adults.

Drug Interactions

Table 3 summarizes level 1 (major) and 2 (moderate) drug interactions cited in interaction reports.

Table 3* Level 1 and level 2 drug interactions

Precipitant drug	Object drug†		Description
Cimetidine	Zolmitriptan	↑	Following coadministration with cimetidine, the half-life and AUC of a 5 mg dose of zolmitriptan and its active metabolite may be doubled.
Ergot alkaloids (dihydroergotamine, methysergide)	5-HT_1 agonists	↑↓	The risk of vasospastic reactions may be increased. Use of 5-HT_1 agonists within 24 hours of treatment with an ergot-containing medication is contraindicated.
Azole antifungals/CYP3A4 inhibitors (eg, ketoconazole, itraconazole)	Almotriptan Eletriptan	↑	Coadministration of almotriptan and ketoconazole (400 mg/day for 3 days) may result in a ≈60% increase in AUC and maximal plasma concentration of almotriptan. The AUC and C_{max} of eletriptan are increased with coadministration. Do not use eletriptan within 72 hours of treatment with a potent CYP3A4 inhibitor.
MAOIs	Almotriptan Rizatriptan Sumatriptan Zolmitriptan	↑	Use of certain 5-HT_1 agonists concomitantly with or within 2 weeks following the discontinuation of an MAOI is contraindicated. If it is necessary to use such agents together, naratriptan, eletriptan, and frovatriptan appear to be less likely to interact with MAOIs.
Propranolol	Rizatriptan	↑	In a study of coadministration of propranolol 240 mg/day and a single dose of rizatriptan 10 mg in healthy subjects, mean plasma AUC for rizatriptan was increased by 70% during propranolol administration, and a 4-fold increase was observed in 1 subject.
Sibutramine	Sumatriptan‡	↑	A "serotonin syndrome," including CNS irritability, motor weakness, shivering, myoclonus, and altered consciousness may occur. Monitor the patient for adverse effects if concurrent use cannot be avoided.
Sumatriptan‡	Fluoxetine Sertraline Nefazodone Venlafaxine	↑	There have been rare reports of weakness, hyperreflexia, and incoordination with combined use of serotonin reuptake inhibitors. If concomitant treatment is clinically warranted, observe the patient carefully.

*Adapted from reference 4

† ↑ = Object drug increased. ↓ = Object drug decreased

‡ Based on pharmacologic and pharmacokinetic considerations, similar interactions may occur with other triptans not listed

Adverse Drug Events

The triptans differ from one another in terms of tolerability. The most frequent side effects are tingling, paresthesias, and sensations of warmth in the head, neck, chest, and limbs; less frequent are dizziness, flushing, and neck pain or stiffness. Triptans can constrict coronary arteries and may cause chest symptoms, which may mimic angina pectoris. In rare instances, triptan therapy has been associated with myocardial infarction.[1,5-12]

Occurrence of adverse drug events is generally dose related. Table 4 summarizes adverse events pooled from separate studies. These adverse events are not necessarily comparable among each triptan.

Table 4. Oral 5-HT$_1$ Agonist Adverse Reactions (%)*

Adverse Event	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan	Almotriptan	Frovatriptan	Eletriptan
Atypical sensations							
Hypesthesia	--	--	--	1	--	--	--
Paresthesia	1-2	3-4	3-5	5-9	1	4	3-4
Hot/Cold sensation	--	--	--	--	--	3	--
Warm/Cold sensation	--	--	2-3	--	--	--	--
Warm/Hot sensation	--	--	--	5-7	--	--	2
Miscellaneous sensations	2-4	4-5	--	--	--	--	--
CNS							
Asthenia	--	--	--	3-9	--	--	4-10
Dizziness	1-2	4-9	> 1	6-10	--	8	3-7
Drowsiness	1-2	--	> 1	--	--	--	--
Fatigue	2	4-7	2-3	--	--	5	--
Headache	--	< 2-2	> 1	--	--	4	3-4
Myasthenia	--	--	--	0	--	--	--
Somnolence	--	4-8	--	5-8	--	--	3-7
Vertigo	--	--	< 1	0	--	--	--
Miscellaneous CNS effects	4-7	--	--	--	--	--	--
Pain/Pressure sensations							
Chest tightness pressure, and/or heaviness	--	< 2	1	2	--	2	1
Heaviness	--	--	< 1	1	--	--	--
Neck/Throat/Jaw	1-2	< 2-2	< 1-3	4-10	--	--	--
Pain, location specified/ unspecified	--	6	2	2-3	--	--	--
Pressure	--	--	< 1-2	--	--	--	--
Regional pain	--	< 1	--	--	--	--	--
Tightness	--	--	< 1-2	--	--	--	--
Skeletal	--	--	--	--	--	3	--
Other	2-4	3	1-3	2-3	--	--	--
GI							
Dry mouth	--	3	> 1	3-5	1	3	2-4
Dyspepsia	--	--	--	3	--	2	1-2
Dysphagia (including throat tightness/difficulty swallowing)	--	--	--	0-2	--	--	1-2
Abdominal pain/ discomfort/stomach pain/cramps/ pressure	--	--	--	--	--	--	1
Nausea	4-5	4-6	--	4-9	1-2	--	4-8
Miscellaneous							
Myalgia	--	--	--	1	--	--	--
Palpitations	--	--	> 1	0	--	--	--
Sweating	--	--	--	0	--	--	--
Other	6-7	--	--	--	--	--	--
Flushing	--	--	--	--	--	4	2

*Adapted from reference 4

Triptans are contraindicated in the following circumstances:[4-12]

- ischemic heart disease (angina pectoris, history of MI, strokes, transient ischemic attacks [TIAs], or documented silent ischemia)
- Prinzmetal variant angina or other significant underlying cardiovascular disease
- patients with signs or symptoms consistent with ischemic heart disease or coronary artery vasospasm;
- patients with uncontrolled hypertension
- concurrent use of (or use within 24 hours of) ergotamine-containing preparations or ergot-type medications such as dihydroergotamine or methysergide
- concurrent monoamine oxidase inhibitor (MAOI) therapy (or within 2 weeks of discontinuing an MAOI [except for eletriptan, frovatriptan and naratriptan];see Drug Interactions)
- within 24 hours of another triptan
- management of hemiplegic or basilar migraine
- ischemic bowel disease
- hypersensitivity to the product or any of its ingredients

Dosing and Administration

Table 5 summarizes the recommended dosage range and maximum daily dose of each triptan. Per package labeling, the safety of treating an average of more than 4 migraine attacks in a 30 day period with a triptan has not been established. The package labeling for eletriptan (Relpax) and zolmitriptan (Zomig) state that the safety of treating an average of more than 3 migraine attacks in a 30 day period has not been established.

Table 5. Triptan Dosing Recommendations[5-12]

Generic Name	Brand Name Example(s)	Dosage*	Maximum Daily Dosage
Sumatriptan Injection	**Imitrex**	6 mg/0.5ml	12 mg (1ml)
Sumatriptan tablets		25 mg-**100 mg**	200 mg
Sumatriptan Nasal		5mg – 20 mg	40 mg
Naratriptan	**Amerge**	1 mg - **2.5 mg**	5mg
Zolmitriptan	Zomig, Zomig ZMT (disintegrating tablet)`	2.5 mg - **5 mg**	10mg
	Zomig Nasal	5 mg/unit	
Rizatriptan benzoate	Maxalt	5 – **10 mg**	30mg
Rizatriptan benzoate-MLT	Maxalt-MLT (disintegrating tablet)		
Almotriptan	Axert	6.25 mg **-12.5 mg**	25 mg
Frovatriptan	Frova	2.5 mg	7.5 mg
Eletriptan	Relpax	20 mg – **40 mg**	80 mg

*Dosages in **bold** provided greater headache response in controlled clinical trials

Effectiveness

Numerous outcome measures have been used in clinical studies to determine the efficacy of triptans. Some of these measures include 2 hour headache response, speed of headache response, sustained headache response, relief of other migraine symptoms (e.g., nausea, vomiting, photophobia), patient preference and satisfaction, health related and quality of life and adverse effects. The International Headache Society recommends the use of patient free response at 2 hours as the primary measure of efficacy. However, many clinical trials use headache response as the primary outcome measure. With this measure patients typically must wait until they have a moderate to severe headache before taking a study medication. Two hours post administration of the triptan, the patient rates the severity of the headache again. The response

is defined as a reduction in headache from "moderate " or "severe" to "mild" or "none". Criticisms of this measure exist and include that a 2-hour response may not be as important to the patient as other measures such as time to response or pain free response.

Tables 6 and 7 provide a comparison of response rates of triptans to placebo. These trials do not directly compare triptan to triptan but provide info on how the triptans improved headache response. While the placebo response rate in these trials was high (ranging from 16% to 44%), triptan treatment provided a statistically significant superior response rate compared to placebo.

Table 6. Two-hour response rate

Triptan	Placebo	Triptan*
Sumatriptan 25 mg	17-27%	52%
Sumatriptan 50 mg		50-61%
Sumatriptan 100 mg		56-62%
Zolmitriptan 1 mg	16-44%	27-50%
Zolmitriptan 2.5 mg		62-65%
Zolmitriptan 5 mg		59-67%
Rizatriptan 5 mg	23-40%	60-63%
Rizatriptan 10 mg		67-71%
Almotriptan 6.25 mg	33-40%	55.4-55.6%
Almotriptan 12.5 mg		58.5-64.9%
Frovatriptan	21-27%	37-46%
Eletriptan 20 mg	19-39.5%	47.3-54.3%
Eletriptan 40 mg		53.9-65%
Eletriptan 80 mg		58.6-77.1%

*Statistically significant in comparison with placebo

Table 7. Four-hour response rate

Triptan	Placebo	Triptan*
Sumatriptan 25 mg	19-38%	65-67%
Sumatriptan 50 mg		68-78%
Sumatriptan 100 mg		71-79%
Naratriptan 1 mg	27-34%	50-54%
Naratriptan 2.5 mg		60-66%

*Statistically significant in comparison with placebo

The results of a meta-analysis published in *Lancet* in 2001[14] are summarized in Table 8. This analysis was conducted on data from 53 clinical trials (41 published, 12 unpublished). Data included were from double-blind randomized, placebo controlled or active-controlled clinical trials of marketed or soon to be marketed triptans (at that time) at clinical doses. Sumatriptan 100 mg was used as the reference dose. The results from this meta-analysis indicated that rizatriptan 10 mg was superior to sumatriptan 100mg in terms of sustained freedom of pain and consistency of effect. Pain relief and sustained freedom from pain with eletriptan 80 mg compares favorably to sumatriptan 100mg but with less tolerability. Almotriptan 12.5 mg provided better sustained freedom from pain and consistency of effect, along with good tolerability.

Table 8. Ferrari, et al., 2001 Meta Analysis[14]

Product	Dosage	*In Comparison with 100mg Sumatriptan Tablet*			
		Relief at 2 hr*	**Sustained Pain Free†**	**Consistency Of Effect‡**	**Tolerability**
Sumatriptan	25 mg	-	=/-	-	+
	50 mg	=	=	=/-	=
Naratriptan	2.5	-	-	-	++
Zolmitriptan	2.5 mg	=	=	=	=
	5 mg	=	=	=	=
Rizatriptan	5 mg	=	=	=	=
	10 mg	+	+	++	=
Almotriptan	12.5 mg	=	+	+	++
Eletriptan	20 mg	-	-	-	=
	40 mg	=/+	=/+	=	=
	80 mg	+	+	=	-

= equivalent; - less effective; + more effective; ++ much more effective
*composite endpoint of pain response and pain freedom at 2 hours post dose
†Composite endpoint of pain freedom by 2hrs post dose and for 24 hours after one dose without use of rescue medication
‡Effective in at least 2 of 3 attacks

The Oregon Evidence Based Practice Center identified and assessed peer-reviewed studies and produced evidence-based reviews on triptan therapy. Included in this comprehensive review were results of triptan head to head studies. Table 10 summarizes results of the measurements 2 hour pain relief, 2 hour pain free, and 24 hour sustained relief.

Table 10* Results of triptan head to head trials[16-23]

		% of Patients with 2 Hour Pain Relief							
Ref.	**P value**	**R5**	**R10**	**S25**	**S50**	**S100**	**Z2.5**	**Z5**	**N2.5**
Havanka (4-hr)	NS	-	-	-	-	60	-	-	52
Bomhof	<0.001	-	68.7	-	-	-	66.8	-	48.4
Pascual	NS	-	70.5	-	-	-	66.8	-	-
Tfelt-Hansen	NS	60	67	-	-	62	-	-	-
Lines	NS	63	-	-	67	-	-	-	-
Geraud	NS	-	-	-	-	61	-	59	-
Gallagher	<0.001	-	-	66.2	67.9	-	72.2	72.2	-
Gruffyd-Jones	NS	-	-	-	66.6	-	62.9	65.7	-

		% of Patients with 2 Hour Pain Free							
Ref.	**P value**	**R5**	**R10**	**S25**	**S50**	**S100**	**Z2.5**	**Z5**	**N2.5**
Bomhof	<0.001	-	44.8	-	-	-	-	-	20.7
Pascual	<0.05	-	43.2	-	-	-	35.6	-	-
Tfelt-Hansen	<0.05	25	40	-	-	33	-	-	-
Lines	NS	22	-	-	28	-	-	-	-
Geraud	NS	-	-	-	-	30	-	29	-
Gruffyd-Jones	NS	-	-	-	35.3	-	32.4	36	-

			% of Patients with 24-Hour Sustained Relief							
Ref.	**P value**	**Response Measurement**	**R5**	**R10**	**S25**	**S50**	**S100**	**Z2.5**	**Z5**	**N2.5**
Havanka	NR	Sustained	-	-	-	-	44	-	-	48
Bomhof	NR	Recurrence Rate	-	33	-	-	-	-	-	21
Pascual	NR	Recurrence Rate	-	28	-	-	-	29	-	-
Gallagher	<0.001	Sustained	-	-	33.1	-	-	40.7	42.5	-
Gruffyd-Jones	NR	Recurrence Rate	-	-	-	30.6	-	30.3	29.9	-

*adapted from reference 16
R5/R10 = Rizatriptan 5mg and 10mg
S25/S50/S100 = Sumatriptan 25mg, 50mg, and 100mg
Z2.5/Z5=Zolmitriptan 2.5mg and 5.0mg
N5=Naratriptan 5mg

Additional findings from the OHSU triptan review of four head-to-head trials that compared recommended dosages of triptan include (NNT=number needed to treat):

- Naratriptan 2.5 mg and sumatriptan 100 mg were found to be similar in several efficacy measures except for 4-hour pain relief, for which sumatriptan 100 mg was superior (NNT=6). Adverse events were similar.
- Rizatriptan 10 mg was found to be more efficacious than sumatriptan 100 mg in some efficacy measures (1-hour pain relief (NNT=11), 2-hour pain-free (NNT=14), return to normal function by 1 hour and 2 hours (NNT=9), and nausea-free at 2 hours (NNT=12.5). For other efficacy measures and for adverse events, the two drugs were similar.
- No differences were found between zolmitriptan 5 mg and sumatriptan 100 mg on any efficacy or tolerability measure.
- Rizatriptan 10 mg was found to be more efficacious than sumatriptan 100 mg in some efficacy measures (1-hour pain relief (NNT=9), 1-hour pain free (NNT=16), 2-hour pain relief (NNT=5), 2-hour pain-free (NNT=4), and relief of photophobia (NNT=8). For other efficacy measures and for adverse events, the two drugs were similar.

Numerous treatment attributes contribute to the overall patient acceptability of a drug. Based on population based surveys and using patient satisfaction as a treatment endpoint, the treatment priorities identified by patients include the following[24]:

- rapid pain relief (< 30 min)
- Complete pain relief within 2 hours
- Return to normal function within 1 hour
- Relief of migraine related symptoms (e.g., nausea, photophobia, phonophobia)
- Reduction in headache recurrence
- Predictable efficacy
- Minimal adverse effects (tolerability)
- Oral administration

Tripstar is a scoring system that has been developed to assess a range of drug attributes that will facilitate an evidence based and patient oriented selection of the triptan that most satisfies the needs of an individual patient (the ideal triptan).[25] Recently, a preliminary test of the Tripstar model was performed at the 10th World Congress of the International Headache Society. Selected attributes were based on results from previous community surveys of migraineurs and surveys completed by the conference participants; neurologists, primary care physicians and internists. The attributes included pain freedom at 2 hours, sustained pain freedom, consistency, tolerability and worldwide clinical exposure as a measure of safety. A separate survey was performed for mild and severe migraine. The results for each survey were similar; pain freedom and sustained pain free were weighted slightly greater than consistency and tolerability, whereas worldwide exposure was the least important. Using the Tripstar scoring system, the relative weights of these attributes were combined with the meta-analysis data from Ferrari, et al[5] to determine the ideal triptan. When all 5 attributes were considered, sumatriptan 50 mg and 100 mg and almotriptan 12.5 mg most closely approximated the ideal triptan for mild and severe migraine. If world wide clinical exposure was excluded, almotriptan 12.5 mg most closely resembled the ideal triptan having scored better in terms of pain freedom, sustained pain-free, consistency and tolerability.

Conclusion

All brand products within the class reviewed are effective and well tolerated. Very few head to head trials compare recommended doses of triptans or incorporate multiple endpoints that address the therapeutic attributes or patient preferences as previously outlined. While the pharmacological action of the triptans is similar, their pharmacokinetic profiles are distinct. Differences in pharmacokinetics will affect such parameters as bioavailability, onset of pain relief and duration of pain relief. Preferences among patients with migraine vary and they may respond better to one agent than another.

All brand products within the class reviewed are comparable to each other and offer no significant clinical advantage over each other in general use.

X. Recommendations

No brand triptan is recommended for preferred status.

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Overview

Estrogen supplements, around since the 1940's, are derived from naturally occurring hormones. Science has since formulated synthetic steroidal and non-steroidal compounds with estrogenic activity. The estrogens in the body are regulated by a complex feedback cycle that results in ovulation and menstruation, and at menopause, estrogen production declines. The average age of onset of menopause is estimated to be 51.4 years; however,

earlier loss of ovarian function may occur secondary to ovarian surgery, endocrinologic and autoimmune disorders, and smoking.[1]

Decreased estrogen levels may trigger alterations in the body that result in genitourinary atrophy, vasomotor instability, blood lipid alterations, cardiovascular diseases, insomnia, psychosexual disorders and osteoporosis, thus having an effect on quality of life. Estrogen replacement therapy (ERT) and estrogen plus progestin therapy (HRT) are important to women's health. Because estrogen receptors are located in multiple areas of the body, estrogen has been shown to have additional health benefits beyond vasomotor symptom management, as well as potential risks. As a result of the July 2002 findings from the estrogen / progestin arm of the Women's Health Initiative (WHI) trial, the Food and Drug Administration (FDA) has updated label warnings on all estrogen products, and several professional organizations have recommended against use of estrogen and combination products for the prevention of chronic conditions. In 1999, estrogens were the number one prescribed drug class for women aged 45-64.[2]

Data places the number of women in the United States over the age of 50 years, at 50 million.[1] Given the current life expectancies, women can expect to live one-third of their life span after the onset of menopause. In 2002, national Medicaid use of estrogens resulted in 102 prescriptions per 1,000 members.[3] Various estrogen formulations are available, with conjugated equine estrogen being the most common in the United States. Transdermal, intramuscular and topical estrogen treatments are alternatives with differing hormonal compositions and consequences of first-pass metabolism. This review encompasses all dosage forms and strengths.

Evidence-Based Medicine and Current Treatment Guidelines

In postmenopausal women, estrogens are effective for treating vasomotor symptoms, vaginal atrophy and they also help prevent bone loss associated with osteoporosis. However, with the introduction of the 2002 Women's Health Initiative (WHI) results and growing use of evidence-based medicine, many medical organizations now suggest that ERT / HRT be used only for management of vasomotor symptoms, using the lowest dose for the shortest duration. Topical vaginal products should especially be considered when ERT / HRT is only being considered for the treatment of vaginal atrophy. In addition, labeling for Premarin has been updated to reflect the following changes:[4]

- Other non-estrogen therapies should be carefully considered if ERT / HRT is being used for the sole purpose of osteoporosis prevention.
- Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

A number of recent studies, including the WHI trial, have played an important role in the current treatment recommendations for ERT / HRT in postmenopausal women. Treatment with ERT / HRT, now more than ever, is a decision to be made on an individual basis. The following are significant findings from several recent studies.

Women's Health Initiative (WHI)[5-15]

The Women's Health Initiative 15-year, three-part, research program of 162,000 American women, was established to address the common causes of death, disability and poor quality of life in postmenopausal women. The program documented findings on cardiovascular

disease, cancer and osteoporosis. In July 2002, researchers stopped the estrogen plus progestin arm of the study after the findings suggested the associated health risks outweighed the benefits, and concluded combined estrogen and progestin therapy is not suitable for the prevention of chronic diseases. Researchers are continuing to report data from other arms of the study (Premarin only) and final results will be released in 2005. The following outcomes from the estrogen plus progestin (Prempro) study (n=16,608) have been influential in the treatment of postmenopausal women:

- 24% reduction in all fractures and a 33% reduction in hip fractures.
- Increase in hipbone density 3.7% after 3 years of treatment compared to 0.14% for placebo.
- 19% decrease in endometrial cancer and 58% increase in ovarian cancer rates.
- 24% overall increase in the risk of coronary heart disease.
- 81% increased risk of heart disease in the first year after starting treatment.
- 24% increase risk for breast cancer due to treatment.
- For every 10,000 women followed for 1 year, one would expect to see 31 strokes in women on estrogen plus progestin compared to 24 with placebo. (31% increase in the risk for stroke).
- There were no clear benefits in the estrogen plus progestin study group on any of the quality of life measures.

Hormonal replacement after breast cancer-is it safe? A randomized comparison: HABITS trial stopped.[16]

A safety analysis study, one of two studies started to evaluate hormone replacement therapy safety in 345 women with previous breast cancer, was stopped early, as reported in the February 2004 issue of *The Lancet*. Women were randomized to 2 years of hormone replacement therapy or best symptomatic treatment without hormones (no HRT). The primary endpoint was any new breast cancer event. Early findings showed that 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. The trial was stopped when these findings were discovered and determined to be an unacceptable risk for women exposed to HRT.

Hormone Therapy and the Progression of Coronary-Artery Atherosclerosis in Postmenopausal Women (Well-HART Trial)[17]

The Women's Estrogen-Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial was a double-blind, placebo-controlled trial of 225 postmenopausal women, who were randomized to usual care with estrogen or estrogen plus progestin (medroxyprogesterone). Women were included if they were 75 years of age or younger, had LDL levels of 100-250mg per deciliter, triglyceride levels of less than 400mg per deciliter, and had at least one coronary-artery lesion occluding 30% or more of the luminal diameter. Primary outcome measure was the average per-participant change between baseline and follow-up coronary angiograms in the percent stenosis measured by quantitative coronary angiography. The mean change in the percent stenosis was 1.89 ± 0.78 percentage points in the control group, 2.18 ± 0.76 in the estrogen group, and 1.24 ± 0.80 in the estrogen plus progestin group. These results showed that estrogen or estrogen plus progestin has no significant effect on the progression of atherosclerosis in postmenopausal women.

Heart, Estrogen/Progestin Replacement Study[18]

The Heart, Estrogen/Progestin Replacement Study (HERS) was the first large randomized, placebo-controlled clinical trial that looked at the effect of HRT on women with heart disease. The study involved 2,763 women average age 67, who were treated with HRT for 4 years. The results of the study showed that HRT did not prevent further heart attacks or death from coronary heart disease in women with pre-existing heart disease. This outcome occurred despite an 11% reduction in LDL cholesterol and an increase by 10% in HDL

cholesterol levels. Increased risk of deep venous thrombosis and pulmonary embolism was also documented with HRT. Investigators concluded women with heart disease should not be started on HRT to prevent heart attacks until data from on-going trials is available.

Postmenopausal Estrogen/Progestin Interventions Trial[19]

The Postmenopausal Estrogen / Progestin Interventions Trial (PEPI), sponsored by the National Heart, Lung, and Blood Institute and other units of the National Institutes of Health, was conducted over 3 years and involved 875 women, ages 45-64. PEPI tested four hormone regimens: estrogen alone, taken daily; estrogen taken daily with medroxyprogesterone, for 12 days a month; estrogen plus medroxyprogesterone taken daily; and estrogen taken daily plus micronized progesterone, for 12 days a month. The study evaluated ERT / HRT and heart disease risk factors, but was not large or long enough to fully evaluate the long-term effects. The key findings were that each of the hormone therapies improved key heart disease risk factors: increase in HDL and a decrease in LDL and fibrinogen. The study also showed slowed bone loss and significant increase in bone mass.

Endometrial effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate: two-year substudy results. [20]

This study reports the endometrial results from patients enrolled in a subset of the Women's HOPE (Health and Osteoporosis, Progestin and Estrogen) Study. The study looked at the endometrial safety of 2 years of lower doses of continuous combined estrogen and medroxyprogesterone. Eight hundred and twenty-two study participants were taken from 19 centers across the United States, and were randomized to estrogen alone, estrogen plus progestin or placebo. Results showed that two years of treatment with lower doses of the estrogen plus progestin combination provided endometrial protection comparable to that seen with commonly prescribed dosages. Risk of endometrial hyperplasia in patients who took estrogen alone, was shown to increase with dose and duration.

Treatment Guidelines and Recommendations

U.S. Preventative Services Task Force 2002[21]
1. The U.S. Preventative Services Task Force has recommended against the routine use of estrogen and progestin for the prevention of chronic conditions in postmenopausal women. The committee did not evaluate the use of HRT to treat vasomotor or urogenital symptoms, but recommend the benefits and harms of treatment be balanced with individual preferences, risks for chronic diseases, and presence of menopausal symptoms. 2. There is insufficient evidence to recommend for or against the use of unopposed estrogen for the prevention of chronic conditions in postmenopausal women who have had a hysterectomy.

American Association of Clinical Endocrinologists[22]
1. Menopausal hormone therapy must be individualized taking into consideration the benefits, risks, and alternatives. It is essential for a woman contemplating menopausal hormone therapy to discuss these issues with her physician. 2. Menopausal therapy is appropriate for women with moderate to severe vasomotor symptoms associated with estrogen deficiency, quality of life symptoms resulting from estrogen deficiency, and significant symptoms related to vaginal atrophy. 3. Strong consideration should be given to alternative pharmacologic therapy options for prevention and treatment of osteoporosis in patients not electing to take menopausal hormone therapy.

4. Menopausal therapy is not indicated solely for the primary or secondary prevention of cardiovascular disease.
5. Hormone therapy should be at the minimum dose that improves symptoms and used for only so long as symptoms remain significant when assessed intermittently off of therapy.

The North American Menopause Society[23]
1. Progestin should be added to estrogen therapy in all postmenopausal women with an intact uterus to prevent the elevated risk of estrogen-induced endometrial hyperplasia and adenocarcinoma. All U.S. FDA approved progestin formulations will provide endometrial protection if the dose and duration are adequate. Evidence is lacking to recommend topical progesterone for preventing estrogen-induced endometrial hyperplasia.

Institute For Clinical Systems Improvement[24]
1. ICSI guidelines focus on the management of symptoms and conditions commonly associated with menopause, with emphasis on the role of hormone therapy relative to other available options. Although hormone therapy is often the most effective treatment for menopausal symptoms, it is not always necessary. 2. Women using hormone therapy must be regularly evaluated regarding their continued requirements for treatment, especially if there has been any change in their overall health status. 3. Women who have recently discontinued hormone therapy are at risk for rapid bone loss and must be identified and monitored to ensure continued bone health. 4. The role of hormone replacement therapy in disease prevention has been all but eliminated in current practice. 5. The exact risks with hormone therapy, as well as side effects, may not be fully defined, but they cannot be dismissed and must always be considered and discussed as part of the collaborative decision-making process. 6. Careful consideration and in-depth discussion are required for the initiation or continuation of hormone therapy, based on individual values and priorities, as well as risks and benefit.

Food and Drug Administration[25]
1. Hormones should not be taken for cardiovascular protection. 2. If ERT / HRT is being used for osteoporosis prevention, consideration should be given to taking other alternative treatments that have not been shown to increase the risk of breast cancer. 3. Women looking to discontinue treatment who have had success in treating vasomotor symptoms, should do so slowly over time-possibly as long as 6 months. 4. All women taking ERT / HRT should speak to their physicians about the risks and benefits of continuing treatment. 5. In late February 2004, the FDA also asked manufacturers of hormone replacement therapies to add a warning to their labels-that hormone replacement may increase older women's risk of Alzheimer's disease or other types of dementia, another change from what was previously believed.

Estrogen Replacement Products (AHFS Class 681604) Single Entity Agents

Comparative Indications for the Single Entity Estrogen Products

Table 1 lists the estrogen products included in this review. This review encompasses all dosage forms and strengths.

Table 1. Estrogen Products in this Review

Formulation	Generic Name	Example Brand Names (s)
Oral Estradiol	Estradiol	Estrace, estradiol*, Gynodiol
Oral Conjugated Estrogens	Conjugated Estrogens	Premarin
	Conjugated Estrogens (Synthetic)	Cenestin
Oral Esterified Estrogens	Esterified Estrogens	Menest
Oral Estropipate	Estropipate	Estropipate*, Ogen, Ortho-Est
Transdermal Estradiol	Estradiol	Alora, Climara, Esclim, Estraderm, Estradiol*, Vivelle/ Dot
Vaginal Estradiol	Estradiol	Estrace Cream, Estring, Vagifem, Femring
Vaginal Conjugated Estrogens	Conjugated Estrogens	Premarin Cream
Vaginal Estropipate	Estropipate	Ogen Cream
Injectables	Conjugated Estrogens	Premarin Intravenous
	Estradiol Cypionate	Depo-Estradiol, Depogen^
	Estradiol Valerate	Delestrogen, Dioval^, Valergen^
	Estrone	Kestrone^

*Indicates generic available; ^ indicates product no longer available

The indications for the estrogen replacement products vary by formulation. All of the oral and transdermal products are approved for use in the treatment of vasomotor symptoms. Vaginal products offer local effects as the drug is readily absorbed by the vaginal epithelium. Injectable estrogens are less commonly used due to fluctuations in plasma concentrations and poor patient acceptance. The following tables (2,3, 4 and 5) summarize the FDA-approved indications for the oral, transdermal, vaginal and injectable products in this review.

Table 2. FDA-Approved Indications for the Oral Estrogen Products[4, 26-31]

Brand Name	Vasomotor Symptoms	Atrophic Vaginitis	Kraurosis Vulvae	Hypo-gonadism	Castration	Primary Ovarian Failure	Breast Cancer	Osteoporosis Prevention	Prostate Cancer
Cenestin	✔ (0.625, 0.9 and 1.25mg)	✔ (0.3mg)							
Estrace	✔	✔		✔	✔	✔	✔	✔	✔
Gynodiol	✔	✔		✔	✔	✔	✔	✔	✔
Menest	✔	✔	✔	✔	✔	✔	✔		✔
Ogen	✔	✔		✔	✔	✔		✔	
Ortho-Est	✔	✔		✔	✔	✔		✔	
Premarin	✔	✔		✔	✔	✔	✔	✔	✔

Table 3. FDA-Approved Indications for the Transdermal Estrogen Products[32-37]

Indication	Vasomotor Symptoms	Atrophic Vaginitis	Kraurosis Vulvae	Atrophic Urethritis	Hypo-gonadism	Primary Ovarian Failure	Castration	Osteoporosis Prevention
Alora	✔	✔			✔	✔	✔	✔
Climara	✔	✔			✔	✔	✔	✔
Esclim	✔	✔			✔	✔	✔	
Estraderm	✔	✔	✔	✔	✔	✔	✔	✔
Vivelle/Dot	✔	✔			✔	✔	✔	✔

Table 4. FDA-Approved Indications for the Vaginal Estrogen Products[27, 38-42]

Indication	Vasomotor Symptoms	Atrophic Vaginitis	Kraurosis Vulvae	Atrophic Urethritis
Estrace Cream		✔		
Estring Ring		✔		✔
Femring Ring	✔	✔		
Ogen Cream		✔		
Premarin Cream		✔	✔	
Vagifem Tablet		✔		

Table 5. FDA-Approved Indications for the Injectable Estrogen Products[43-45]

Indication	Vasomotor Symptoms	Atrophic Vaginitis	Hypogonadism	Castration	Primary Ovarian Failure	Prostate Cancer	Uterine Bleeding
Delestrogen	✔	✔	✔	✔	✔	✔	
Depo-Estradiol	✔		✔				
Premarin							✔

Pharmacokinetic Parameters of the Estrogen Products

Absorption

Estrogens used in replacement therapy are well absorbed through the skin, mucous membranes, and gastrointestinal tract. Natural progesterone is poorly absorbed orally, so synthetic forms such as medroxyprogesterone are used clinically.[46] The drug delivery formulation largely drives the main differences among the pharmacokinetic properties in the estrogen therapy class. Minor differences exist between the different formulations, leaving product choice to be based on personal preference, compliance issues and specific symptoms. Limited pharmacokinetic information is available for some of the estrogen products. Local applications, such as vaginal drug formulations, may be absorbed sufficiently to cause systemic effects.[46]

Distribution, Metabolism and Elimination

Estrogens circulate in the blood and are 50-80% bound to sex-hormone-binding globulin (SHBG) and albumin.[47] Complex metabolic processes continually equilibrate conjugated and unconjugated estrogens where a proportion of estrogen is excreted into the bile and reabsorbed in the intestine. During this enterohepatic recirculation, estrogens and their metabolites undergo degradation, oxidation and conjugation and are primarily excreted in the urine.

Oral naturally occurring estrogens are extensively metabolized in the liver through the first-pass effect, and 60-90% is converted to estrone, a less potent estrogen.[1] Higher doses of exogenous estrogens must be administered to account for this effect. Synthetic estrogens, such as ethinyl estadiol, are metabolized slowly by the liver, and exhibit higher

potency. Non-oral drug formulations, such as transdermal patches, are not subject to first-pass metabolism and require lower total doses. In addition, transdermal estrogen delivery has no effect on the production of certain proteins thought to be responsible for some adverse effects of oral estrogen therapy.

Table 6 displays the pharmacokinetic principles discussed above for some of the oral, transdermal, vaginal and injectable formulations.

Table 6. Pharmacokinetic Parameters of Select Estrogen Products[4, 25, 31-33, 35-38]

Parameter	Time to Reach Peak Concentration (T_{max})	Protein Binding	Metabolism	Elimination	Half-Life ($T_{1/2}$)
Cenestin	5.8-8.25 hours	-	First-pass in the liver	Primarily Urine	9.7-10.6 hours
Premarin 0.625mg	6.2-8.8 hours	-	First-pass in the liver	Primarily urine	10.1-15 hours
Alora	18 hours	-	Skin, Liver	Urine	1.75 $\pm$ 2.87 hours
Climara	24 hours	-	Skin, Liver	Urine	4 hours
Esclim	27 hours	-	Skin, Liver	Urine	-
Vivelle	12 hours	-	Skin, Liver	Urine	4.4 $\pm$ 2.3 hours
Vivelle-Dot	12 hours	-	Skin, Liver	Urine	5.9-7.7 hours
Estring	0.5-1 hour	-	Liver	Urine	-
Femring	<1 hour	-	Liver	Urine	-

Estrogen Drug Interactions

There are no clinically significant drug interactions that make one estrogen product advantageous over another. In fact, there are no rapid onset, major severity (level 1) drug interactions that have been documented with estrogens.[48] Since estrogens are metabolized similarly, they have drug interactions that are common as a therapy class.

Studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4) and may be affected by either inducers or inhibitors of this enzyme.[48] Inducers, which may reduce plasma concentrations of estrogens and result in lower therapeutic effects and/or changes in the uterine bleeding, include St. John's Wort, phenobarbital, carbamazepine, and rifampin. Inhibitors that may increase plasma concentrations of estrogens are erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice. Dosage adjustments (increased or decreased) may be required to manage the induction or inhibition of estrogens when given in combination with interacting drugs.

Table 7 is a description of the clinically significant estrogen drug interactions with ratings of level 2 (moderate, suspected). Other less severe interactions have been documented including the following: anticoagulants, tricyclic antidepressants, grapefruit juice, cimetidine, ascorbic acid, succinylcholine, and the nonnucleoside reverse transcriptase inhibitors.

Table 7. Clinically Significant Estrogen Drug Interactions [48]

Significance	Interaction	Mechanism
2 (delayed)	Estrogens and Barbiturates	Induction of hepatic enzymes by barbiturates increases elimination of estrogenic substances, thereby decreasing plasma concentrations.
2 (delayed)	Estrogens and Corticosteroids	Inactivation of cytochrome P450, causing decreased formation of the 6-betahydroxy metabolite of prednisolone and possible toxic effects of corticosteroids.
2 (delayed)	Estrogens and Hydantoins	Induction of hepatic enzymes causes increased metabolism of estrogen compounds. Protein binding of phenytoin may be affected.
2 (delayed)	Estrogens (ethinyl estradiol) and Modafinil	Induction of GI and hepatic metabolism (CYP3A4/5) of ethinyl estradiol by Modafinil, causing lowered estrogen efficacy.
2 (delayed)	Estrogens and Rifampin	Metabolism of estrogens in the liver is increased 4-fold.
2 (delayed)	Estrogens and Thyroid Hormones	Estrogens may induce serum thyroxine and thyrotropin, causing an increased need for thyroid hormone.
2 (delayed)	Estrogens and Topiramate	Topiramate increases the metabolism of estrogens.

Adverse Drug Events for the Single Entity Estrogen Products

Although some adverse events have been reported in patients receiving estrogens, most of the serious adverse effects of oral contraceptives (thromboembolic disorders and hepatocellular adenoma) have not been associated with postmenopausal estrogen therapy. This is perhaps a result of comparatively low dosages of estrogens used in ERT. Hormones used in larger doses, for the treatment of breast cancer and prostate cancer, result in an increased risk of serious adverse effects.[47] With the new treatment guidelines for ERT, to treat with the lowest dose possible, the risk of adverse events is minimized.

Little differences exist between the different estrogen combination products. Some patients may tolerate transdermal ERT better due to a lack of production of hepatic proteins, renin substrate, sex-hormone-binding globulin, thyroxine-binding globulin, and cortisol-binding globulin. Elevations in these proteins may be associated with some of the adverse effects of oral estrogens.[1] However, the most common adverse events reported with transdermal products are application site reactions, which may make this dosage form more troublesome for women with sensitive skin.

The following tables list adverse reactions reported for the single entity estrogen products. Incidences of adverse effects are listed as percentages with the placebo incidence listed in parentheses.

Table 8. Common Adverse Events (%), by System, Reported for the Oral Estrogen Products[4, 26-31]

Adverse Event	Cenestin	*Estrace*	Gynodiol	Menest	Ogen	Ortho-Est	Premarin
Body as a Whole							
Headache	68 (67)	✔	✔	✔	✔	✔	26-32 (28)
Back Pain	14 (13)	N/A	N/A	N/A	N/A	N/A	13-14 (12)
Digestive System							
Nausea	0 (2)	✔	✔	✔	✔	✔	6-9 (9)
Gastroenteritis	7 (2)	✔	✔	✔	✔	✔	✔
(vomiting)	28 (23)	✔	✔	✔	✔	✔	15-17 (11)
Abdominal Pain							
Nervous System							
Insomnia	42 (48)	N/A	N/A	N/A	N/A	N/A	6-7 (10)
Emotional Lability	1 (4)	N/A	N/A	N/A	N/A	N/A	N/A
Nervousness	28 (42)	N/A	N/A	N/A	N/A	N/A	2-5 (2)
Depression	28 (38)	✔	✔	✔	✔	✔	5-8 (7)
Respiratory System							
URI (bronchitis)	3 (2)	N/A	N/A	N/A	N/A	N/A	9-12 (11)
Sinusitis	3 (0)	N/A	N/A	N/A	N/A	N/A	6-11 (7)
Skin and Appendages							
Rash	4 (6)	✔	✔	✔	✔	✔	4-5 (2)
Alopecia	3 (2)	✔	✔	✔	✔	✔	✔
Nutritional							
Weight Change (+ or -)	0 (2)	✔	✔	✔	✔	✔	✔
Urogenital System							
Breast Pain	29 (15)	✔	✔	✔	✔	✔	7-12 (9)
Vaginal Bleeding	N/A	✔	✔	✔	✔	✔	2-14 (0)
Dysmenorrhea	6 (6)	N/A	N/A	✔	N/A	N/A	✔
Metrorrhea	14 (6)	✔	✔	✔	✔	✔	✔
Other							
Accidental Injury	N/A	N/A	N/A	✔	N/A	N/A	6-12 (9)
↓ Carbohydrate Tolerance	N/A	✔	✔	✔	✔	✔	✔

#Incidence for placebo not available
N/A Incidence not available
✔ Adverse event reported; specific percentages not available

Table 9. Common Adverse Events (%), by System, Reported for the Transdermal Estrogen Products[32-37]

Adverse Event	Alora	Climara	Esclim	Estraderm	Vivelle	Vivelle-Dot
Body as a Whole						
Headache	6-21 (13)	5-18	6-19	✔	36 (30)	14-50 (24)
Back Pain	3-8 (6)	(10)	(22)	N/A	13 (5)	8-11 (6)
		4-9 (6)	2-6 (4)			
Digestive System						
Nausea	3-7 (3)	1-6 (3)	4-11 (2)	✔	✔	0-6 (3)
Gastroenteritis (vomiting)	0-4 (2)	✔	0-6 (2)	✔	✔	0-2 (1)
	1-8 (5)	0-16	2-11 (9)	✔	✔	0-4 (3)
Abdominal Pain		(8)				
Nervous System						
Insomnia	1-5 (8)	N/A	N/A	N/A	N/A	2-6 (6)
Emotional Lability	N/A	N/A	2-8 (2)	N/A	N/A	0-3 (0)
Nervousness	N/A	N/A	N/A	N/A	N/A	N/A
Depression	1-3 (9)	1-8 (0)	✔	✔	✔	0-11 (4)
Respiratory System						
URI (bronchitis)	16-25 (26)	6-17 (8)	N/A	N/A	N/A	5-11 (6)
Sinusitis	7-12 (18)	4-5 (3)	2-4 (7)	N/A	N/A	5-13 (10)
Skin and Appendages						
Rash	3-9 (6)	0.5-6 (6)	2-4 (6)	✔	5 (4)	3-5 (3)
Application site rxn.	6-57 (59)	N/A	5-11 (6)	17 (#)	9 (10)	0-3 (0)
D/C due to appl. site rxn.	N/A	5-8 (12)	0.9 (#)	2 (#)	0.5 (3)	N/A
Nutritional						
Weight Change (+ or -)	0.5-5 (5)	✔	✔	✔	✔	0-9 (2)
Urogenital System						
Breast Pain	7-35 (8)	5-29 (4)	25-47	✔	✔	0-3 (0)
Vaginal Bleeding	9-33 (13)	✔	(4)	✔	✔	0-11 (5)
Dysmenorrhea	N/A	N/A	✔	N/A	N/A	0-7 (0)
Metrorrhea	N/A	✔	2-6 (0)	✔	✔	2-4 (0)
			✔			
Other						
Accidental Injury	N/A	N/A	2-10 (4)	N/A	N/A	N/A
↓ Carbohydrate Tolerance	N/A	N/A	✔	✔	✔	N/A

#Incidence for placebo not available
N/A Incidence not available
✔ Adverse event documented; specific percentages not available

Table 10. Common Adverse Events (%), by System, Reported for the Vaginal Estrogen Products[27, 38-42]

Adverse Event	Estrace	Estring	Femring	Premarin	Vagifem
Body as a Whole					
Headache	✔	13 (#)	7-10 (9)	✔	N/A
Back Pain	N/A	6 (#)	4-6 (4)	N/A	N/A
Digestive System					
Nausea	✔	3 (#)	2-3 (5)	✔	✔
Gastroenteritis (vomiting)	✔	1-3	✔	✔	✔
Abdominal Pain	✔	4 (#)	✔	✔	N/A
Nervous System					
Insomnia	N/A	4 (#)	N/A	N/A	N/A
Emotional Lability	N/A	N/A	N/A	N/A	N/A
Nervousness	N/A	✔	✔	N/A	N/A
Depression	✔	✔	✔	✔	N/A
Respiratory System					
URI (bronchitis)	N/A	5 (#)	4 (6)	N/A	N/A
Sinusitis	N/A	4 (#)	2-4 (2)	N/A	N/A
Skin and Appendages					
Rash	✔	N/A	✔	✔	✔
Nutritional					
Weight Change (+ or -)	✔	✔	✔	✔	N/A
Urogenital System					
Breast Pain	✔	1 (#)	6-11 (2)	✔	✔
Vaginal Bleeding	✔	✔	8-10 (2)	✔	✔
Dysmenorrhea	N/A	N/A	N/A	✔	N/A
Metrorrhea	✔	N/A	✔	✔	N/A
Vaginal discomfort / pain	N/A	5 (#)	1-2 (4)	✔	N/A
Other					
Accidental Injury	N/A	N/A	N/A	N/A	N/A
↓ Carbohydrate Tolerance	✔	N/A	✔	✔	N/A
D/C due to adverse effect	N/A	5.4 (#)	N/A	3.9% (#)	N/A
Family Stress	N/A	2 (#)	N/A	N/A	N/A

#Incidence for placebo not available
N/A Incidence not available
✔ Adverse event documented; specific percentages not available

Table 11. Common Adverse Events (%), by System, Reported for the Injectable Estrogen Products[43-45]

Adverse Event	Delestrogen	Depo-Estradiol	Premarin
Body as a Whole			
Headache	✔	✔	✔
Back Pain	N/A	N/A	N/A
Digestive System			
Nausea	✔	✔	✔
Gastroenteritis (vomiting)	✔	✔	✔
Abdominal Pain	✔	✔	✔
Nervous System			
Insomnia	N/A	N/A	N/A
Emotional Lability	N/A	N/A	N/A
Nervousness	N/A	N/A	N/A
Depression	✔	✔	✔
Respiratory System			
URI (bronchitis)	N/A	N/A	N/A
Sinusitis	N/A	N/A	N/A
Skin and Appendages			
Rash	N/A	N/A	✔
Nutritional			
Weight Change (+ or -)	✔	✔	✔
Urogenital System			
Breast Pain	✔	✔	✔
Vaginal Bleeding	✔	✔	✔
Dysmenorrhea	N/A	N/A	N/A
Metrorrhea	✔	✔	N/A
Other			
Accidental Injury	N/A	N/A	N/A
↓ Carbohydrate Tolerance	✔	✔	N/A

#Incidence for placebo not available
N/A Incidence not available
✔ Adverse event documented; specific percentages not available

Dosing and Administration for the Single Entity Estrogen Products

Recent labeling changes for the estrogen products stress use of the lowest doses possible, limited to the shortest duration consistent with treatment goals and risks for each individual woman. This is especially important when the sole purpose of treatment is for vasomotor symptoms and atrophic vaginitis, where treatment should remain short-term, and should be discontinued as promptly as possible. All patients should be re-evaluated as clinically appropriate at 3-6 month intervals to determine if treatment is still necessary and to make dosage adjustments based on response. In women who have a uterus,

estrogen plus progestin therapy should be initiated. Dosing for the single entity estrogen products is further described for each product in the following tables.

Table 12. Dosing for the Oral Estrogen Products[4, 26-31]

	Availability	Dose /Frequency/Duration
Cenestin (synthetic conjugated estrogens)	0.3mg, 0.625mg, 0.9mg, 1.25mg tablet	Initial: 0.625mg QD. Max: 1.25mg QD.
Estrace (estradiol)	0.5mg, 1mg, 2mg tablet	Vasomotor sympt., vaginal atrophy: 1-2mg QD, given cyclically (3 weeks on and 1 week off) Hypogonadism, castration, ovarian failure: 1-2mg QD Breast cancer: 10mg TID for 3 months Prostate cancer: 1-2mg TID Osteoporosis: 0.5mg QD, given cyclically
Estradiol (generic)	0.5mg, 1mg, 2mg tablets	Vasomotor sympt., vaginal atrophy: 1-2mg QD, given cyclically (3 weeks on and 1 week off) Hypogonadism, castration, ovarian failure: 1-2mg QD Breast cancer: 10mg TID for 3 months Prostate cancer: 1-2mg TID Osteoporosis: 0.5mg QD, given cyclically
Estropipate (generic)	0.75mg, 1.5mg, 3.0mg tablets	Vasomotor sympt: 0.75-6mg QD, given cyclically Vaginal atrophy: 0.75-6mg QD, given cyclically Hypogonadism: 1.5-9mg QD for 3 weeks, followed by a rest period of 8-10 days Castration and ovarian failure: 1.5-9mg for 3 weeks, followed by a rest period of 8-10 days Osteoporosis: 0.75mg QD for 25 days of a 31-day cycle per month
Gynodiol (estradiol)	0.5mg, 1mg, 1.5mg, and 2mg tablet	Vasomotor sympt., vaginal atrophy: 1-2mg QD, given cyclically (3 weeks on and 1 week off) Hypogonadism, castration, ovarian failure: 1-2mg QD Breast cancer: 10mg TID for 3 months Prostate cancer: 1-2mg TID Osteoporosis: 0.5mg QD, given cyclically
Menest (esterified estrogens)	0.3mg, 0.625mg, 1.25mg, 2.5mg tablet	Vasomotor sympt.: 1.25mg daily, given cyclically Atrophic vaginitis and kraurosis vulvae: 0.3-1.25mg QD, given cyclically Hypogonadism: 2.5-7.5mg QD in divided doses for 20 days, followed by a rest period of 10 days Castration and ovarian failure: 1.25mg QD, given cyclically Breast cancer: 10mg TID for 3 months Prostate cancer: 1.25-2.5mg TID
Ogen (estropipate)	0.75mg, 1.5mg, 3.0mg tablets	Vasomotor sympt.: 0.75-6.0mg QD, given cyclically Vaginal atrophy: 0.75-6.0mg QD, given cyclically Hypogonadism: 1.5-9mg QD for 3 weeks, followed by a rest period of 8-10 days Castration and ovarian failure: 1.5-9mg QD for 3 weeks, followed by a rest period of 8-10 days Osteoporosis: 0.75mg QD for 25 days of a 31-day cycle per month
Ortho-Est (estropipate)	0.75 and 1.5mg tablets	Vasomotor sympt: 0.75-6mg QD, given cyclically Vaginal atrophy: 0.75-6mg QD, given cyclically Hypogonadism: 1.5-9mg QD for 3 weeks, followed by a rest period of 8-10 days Castration and ovarian failure: 1.5-9mg for 3 weeks, followed by a rest period of 8-10 days Osteoporosis: 0.75mg QD for 25 days of a 31-day cycle per month
Premarin (conjugated estrogens)	0.3mg, 0.45mg, 0.625mg, 0.9mg, 1.25mg, 2.5mg	Vasomotor sympt.: initial 0.3mg QD, titrated to lowest effective dose, given continuous or cyclic (25 days on followed by 5 days off) Hypogonadism: 0.3-0.625mg QD, given cyclically Castration, ovarian failure: 1.25mg QD, given cyclically Breast cancer: 10mg TID for 3 months Prostate cancer: 1.25-2.5mg TID Osteoporosis*: initial 0.3mg QD based on response, given continuous or cyclically (25 days on followed by 5 days off)

*Only for women with significant risk of osteoporosis and non-estrogen medications must be carefully considered.

Table 13. Dosing for the Transdermal Estrogen Products[32-37, 46]

	Availability	Dose/Frequency/Duration
Alora (estradiol)	0.025mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day patch	Vasomotor sympt., vaginal atrophy, hypogonadism, castration, and ovarian failure: initial dose is 0.05mg/day applied to the skin twice weekly. Osteoporosis: initial dose is 0.025mg/day applied to the skin twice weekly. May be administered continuously in women with an intact uterus, or on a cyclic schedule in women with an intact uterus not using concomitant progestin therapy.
Climara (estradiol)	0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.06mg/day, 0.075mg/day, 0.1mg/day patch	Vasomotor sympt.: initiated at 0.025mg/day applied once weekly, based on response. Osteoporosis: 0.025mg/day applied once weekly.
Esclim (estradiol)	0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day patch	Initial dose: 0.025mg/day patch, applied twice weekly, either continuous or cyclic in women with an intact uterus. Dosing should be based in initial severity of symptoms and response. Decisions to increase dosage should not be made until after the first 2-3 weeks of treatment.
Estraderm (estradiol)	0.05mg/day and 0.1mg/day patch	Initial dose: 0.05mg/day, applied twice weekly, either continuous or cyclic in women with an intact uterus.
Estradiol (generic)	0.05mg/day and 0.1mg/day patch	Initial dose: 0.05mg/day, applied twice weekly, either continuous or cyclic in women with an intact uterus.
Vivelle (estradiol)	0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day patch	Vasomotor sympt., vaginal atrophy: 0.0375mg/day applied twice weekly, either continuously or cyclically in women with an intact uterus. Osteoporosis: 0.025mg/day applied twice weekly, either continuously or cyclically. Attempts to increase dosage should not be made until after the first month of therapy.
Vivelle-Dot (estradiol)	0.025mg/day, 0.0375mg/day, 0.05mg/day, 0.075mg/day, 0.1mg/day patch	Vasomotor sympt., vaginal atrophy: 0.0375mg/day applied twice weekly, either continuously or cyclically in women with an intact uterus. Osteoporosis: 0.025mg/day applied twice weekly, either continuously or cyclically. Attempts to increase dosage should not be made until after the first month of therapy.

Table 14. Dosing for the Vaginal Estrogen Products[27,38-42]

	Availability	Dose/Frequency/Duration
Estrace Cream (estradiol)	0.01% cream, 42.5 gram tube	Initial: 2-4 g QD for 1-2 weeks, then gradually reduce by ½ of initial dose for 1-2 weeks Maintenance: 1g 1-3 times a week
Estring Ring* (estradiol)	2mg vaginal ring (releases estradiol 7.5micrograms/24 hours)	Patients insert the ring, deep into the vagina, where it should remain in place continuously for three months, then be removed. A new ring can be inserted if deemed appropriate.
Femring Ring* (estradiol)	0.05mg/day and 0.1mg/day	Start with lowest dose (the 0.05mg/day ring). Patients insert the ring into the vagina, where it should remain in place for three months, then be removed. A new ring can be inserted if deemed appropriate.
Ogen Cream		
Premarin Cream (conjugated estrogens_	Each gram contains 0.625mg of conjugated estrogens. Combination package: 42.5 gram tube with calibrated applicator. Refill package also available without the applicator.	0.5 to 2 grams intravaginally QD, given cyclically. Short-term use is recommended.
Vagifem Tablet (estradiol)	Each tablet contains 25 micrograms of estradiol. Comes in blister packages of 8 and 18; includes applicators with insert tablets.	Initial dose: One tablet inserted vaginally QD, at the same time, for 2 weeks. Maintenance dose: One tablet inserted vaginally, twice weekly.

*When prescribed in women with a uterus, a progestin should be initiated to reduce the risk of endometrial cancer.

Table 15. Dosing for the Injectable Estrogen Products[43-46]

Indication	Availability	Dose/Frequency/Duration
Delestrogen * (estradiol valerate)	Multiple dose vials: 10mg/ml (5ml) 20mg/ml (5ml) 40mg/ml (5ml)	Vasomotor sympt. and vaginal atrophy: 10-20mg IM Q4 weeks. Hypogonadism, castration, and ovarian failure: 10-20mg IM Q4weeks. Prostrate cancer: 30mg or more IM Q1-2 weeks.
Depo-Estradiol* (estradiol cypionate)	5mg/ml (5ml)	Usual dosage range: 1-5mg IM Q3-4 weeks. Hypogonadism: 1.5-2mg IM Qmonth.
Premarin Intravenous (conjugated estrogens)	25mg vials with 5ml sterile diluent for re-constitution	25mg injected IV or IM Q6-12 hours

*Contains chlorobutanol as a preservative, which can be habit-forming.

Comparative Effectiveness of the Estrogen Products

The two main factors considered when assessing the efficacy of estrogens are: 1) how effective is the product in treating symptoms of menopause; and 2) what are the long-term health risks of treatment? The most recent clinical evidence from the WHI trial and other pivotal studies has been previously presented in this review in section II. At this time, treatment guidelines stress the primary use of ERT for management of the symptoms associated with menopause. Minor differences have been found between the different estrogen products. Randomized, placebo controlled clinical trials have measured the efficacy and risks of treatment with estrogens. Table 16 summarizes additional outcomes data from recently published trials, on the effects of estrogens on vasomotor symptoms, vaginal atrophy, and on the risks of treatment.

Table 16. Additional Outcomes Evidence for Estrogen Products

Study	Sample	Duration	Results
Women's HOPE[4]	n=241 postmenopausal women, mean age 54 years, with moderate-severe vasomotor symptoms	12 weeks	1) When given placebo, conjugated estrogens, or conjugated estrogen with medroxyprogesterone, the result on vasomotor symptoms was: ♦ A statistically significant ($p<0.001$) reduction from baseline (12-13 hot flashes/day), to post treatment (1-5 hot flashes/day), compared to placebo, was observed in the number and severity of symptoms. 2) The effect on vulvar and vaginal atrophy was: ♦ Vaginal maturation indexes at cycles 6 and 13 showed differences from placebo that were statistically significant ($p<0.001$) for both the estrogen and estrogen plus medroxyprogesterone group.
EPAT[50]	n=199 healthy postmenopausal women	2 years	This trial looked at whether unopposed 17beta-estradiol reduces the progression of subclinical atherosclerosis when modified by body mass index (BMI): ♦ There was no significant difference in the estradiol effect on carotid artery intima-media thickness (IMT) progression between postmenopausal women with a BMI <30 versus a BMI of >30 ($p=0.52$). ♦ In study participants that did not receive lipid-lowering therapy, there was significant improvement in IMT with estradiol treatment in both BMI groups ($p=0.48$ for differences between BMI groups.
Effects of transdermal vs. oral estrogen on C-reactive protein[51]	N=21 postmenopausal women	8 week cross over study	Because studies have shown that oral estrogen causes an increase in c-reactive protein (CRP) that implicates a proinflammatory effect, researchers looked at whether the route of administration of estrogen replacement therapy (transdermal estradiol, oral conjugated estrogens or placebo) is a major determinant:

			♦ Transdermal estrogen had no effect on CRP, however, 8 weeks of oral estrogen treatment caused a more than twofold increase in CRP and a significant reduction in IGF-1 (a hepatic-derived anabolic peptide) ($p<0.01$), in the same women. ♦ Oral estrogen increased CRP levels by a first-pass hepatic effect; because CRP is a predictor of adverse prognosis, the route of administration can be an important consideration in minimizing adverse effects and cardiovascular outcomes.

Conclusions

In 2002, estrogen products fell from fourth to ninth place by overall HMO utilization. In contrast, use of osteoporosis products (Fosamax, Evista, Miacalcin and Actonel) increased, with Fosamax rising from 41st to 27th place, among the top 50 prescribed products. As we are now seeing the impact of the results of the estrogen / progestin arm of the WHI study, utilization of the leading single entity estrogen brand, Premarin, has also fallen from 3rd to 5th place.[3]

Treatment with estrogens is completely different than it was five years ago. Estrogens have not exhibited the benefits, such as on cardiovascular health, as once recognized. The completion of the ongoing WHI studies will likely lead to further changes in the treatment of postmenopausal women. ERT must be used only when the risks, benefits and alternative choices for treatment have been individually considered. Hormone therapy should be kept to the minimum dose required to improve menopausal symptoms and for a limited duration, with frequent re-evaluation of the necessity of treatment.

All estrogen products have been shown to be effective for the treatment of symptoms associated with menopause. There are no significant differences in drug interactions or adverse effects when comparing the same dosage forms. Specific drug therapy selection should be individualized. All brand estrogen single entity products are comparable to each other and to the generics and offer no significant clinical advantage over other alternatives in general use.

Recommendations

No brand single entity estrogen product is recommended for preferred status.

Estrogen Replacement Products (AHFS Class 681604) Combination Agents

Comparative Indications for the Estrogen Combination Products

Table 1 lists the estrogen combination products included in this review. This review encompasses all dosage forms and strengths.

Table 1. Combination Estrogen Products in this Review

Formulation	Generic Name	Example Brand Names (s)
Oral Estradiol	Estradiol / Norethindrone Acetate	Activella
	Ethinyl Estradiol / Norethindrone Acetate	FemHRT 1/5
	17 β -Estradiol / Norgestimate	Ortho-Prefest, Prefest
Oral Conjugated Estrogens	Conjugated Estrogens / Medroxyprogesterone	Premphase, Prempro
Oral Esterified Estrogens	Esterified Estrogens / Methyltestosterone	Estratest / H.S.
Transdermal Estradiol	Estradiol / Levonorgestrel	Climara Pro*
	Estradiol / Norethindrone Acetate	Combipatch

*Climara Pro (estradiol/levonorgestrel transdermal system) was FDA approved in November 2003. Per Alabama Medicaid P&T policy, this drug is eligible for review after it has been commercially available for at least 6 months. Climara Pro will therefore be reviewed at a future time.

The indications for the estrogen combination products vary by formulation. All of the available combination products are approved for use in the treatment of vasomotor symptoms. Injectable estrogens are less commonly used due to fluctuations in plasma concentrations and poor patient acceptance. The following tables (2,3 and 4) summarize the FDA-approved indications for the oral, transdermal, and injectable products in this review.

Table 2. FDA-Approved Indications for the Oral Estrogen Combination Products[52-57]

Indication	Vasomotor Symptoms	Atrophic Vaginitis	Kraurosis Vulvae	Hypo-gonadism	Castration	Primary Ovarian Failure	Breast Cancer	Osteoporosis Prevention	Prostate Cancer
Activella	✔	✔						✔	
Estratest/ H.S.	✔								
FemHRT	✔							✔	
Ortho-Prefest	✔	✔						✔	
Prefest	✔	✔						✔	
Premphase	✔	✔						✔	
Prempro	✔	✔						✔	

Table 3. FDA-Approved Indications for the Single Transdermal Estrogen Combination Product[58]

Indication	Vasomotor Symptoms	Atrophic Vaginitis	Kraurosis Vulvae	Atrophic Urethritis	Hypo-gonadism	Primary Ovarian Failure	Castration	Osteoporosis Prevention
Combipatch	✔	✔			✔	✔	✔	

Pharmacokinetic Parameters of the Estrogen Combination Products

Medroxyprogesterone is approximately 90% bound to plasma proteins, but does not bind to sex hormone binding globulin.[4] Metabolism and elimination of this progestin occur primarily in the liver via hydroxylation, with subsequent conjugation and elimination in the urine. Micronized natural progesterone is effective, but requires larger doses due to significant first-pass metabolism.
Table 5 displays the pharmacokinetic principles discussed above for some of the oral, transdermal, and injectable formulations.

Table 5. Pharmacokinetic Parameters of Select Estrogen Combination Products[52-58]

Parameter	Time to Reach Peak Concentration (T_{max})	Protein Binding	Metabolism	Elimination	Half-Life ($T_{1/2}$)
Activella	Estradiol- 5-8 hours Norethindrone- 0.5-1.5 hours	98%	First-pass in the liver	Primarily urine	Estradiol- 12-14 hours Norethindrone- 8-11 hours
Estratest	Esterified estrogens-NA Methyltestosterone – NA	98%	First-pass in the liver	Primarily urine	Esterified estrogens – NA Testosterone – 10-100 mins
FemHRT	1-2 hours	>95%	First-pass in the liver	Primarily Urine	Ethinyl Estradiol- 23.9 hours Norethindrone- 13.3 hours
Prefest/Ortho-Prefest	17 β -Estradiol- 7 hours Norgestimate- 2 hours	99%	First-pass in the liver	Primarily urine	Estradiol- 16 hours Norgestimate- 37 hours
Premphase / Prempro 0.625mg/ 2.5mg	Medroxyprogesterone- 2.8 hours Conjugated Estrogens- 4.6-5.8 hours	Medroxy-progesterone- 90%	First-pass in the liver	Primarily urine	Medroxyprogesterone- 37.6 hours Conjugated Estrogens- 9.9-31.6 hours
Combipatch	Estradiol- 12-24 hours Norethindrone- 24 hours	-	Skin, Liver	Urine	Estradiol- 2-3 hours Norethindrone- 6-8 hours

Combination Estrogen Drug Interactions

Table 6 is a description of the clinically significant estrogen and progestin drug interactions with ratings of level 2 (moderate, suspected). Other less severe interactions have been documented with estrogens including the following: anticoagulants, tricyclic antidepressants, grapefruit juice, cimetidine, ascorbic acid, succinylcholine, and the nonnucleoside reverse transcriptase inhibitors.

Table 6. Clinically Significant Estrogen / Progestin Drug Interactions [48]

Significance	Interaction	Mechanism
2 (delayed)	Levonorgestrel, Norgestrel (progestins) and Hydantoins	Both hydantoin induction of progestin metabolism via CYP3A4 and sex hormone-

		binding globulin synthesis may reduce progestin concentrations.

*Please refer to the Estrogen Single Entity review for estrogen specific drug-drug interactions

Adverse Drug Events for the Estrogen Combination Products

The addition of a progestin to estrogen replacement therapy may result in intolerance in approximately 5% of patients; some may benefit from dosage reductions or a change to another type of progestin. There is no convincing data to support the premise that continuous-combined hormone replacement reduces progesterone-induced adverse events relative to sequential hormone replacement therapy.[1]

The following tables list adverse reactions reported for the estrogen combination products. Incidences of adverse effects are listed as percentages with the placebo incidence listed in parentheses. Please refer to the Estrogen Single Entity drug review for additional discussion on estrogen related adverse drug events.

Table 7. Common Adverse Events (%), by System, Reported for the Oral Estrogen Combination Products[52-57]

Adverse Event	Activella	Estratest/ H.S.	FemHRT	Prefest/Ortho -Prefest	Premphase	Prempro
Body as a Whole						
Headache	11 (6)	✔	39.5 (40)	23 (#)	37 (#)	28-33 (28)
Back Pain	6 (4)	N/A	4.7 (5.3)	12 (#)	16 (#)	12-13 (12)
Digestive System						
Nausea	11 (0)	✔	7.4 (5.3)	6 (#)	11 (#)	7-10 (9)
Gastroenteritis (vomiting)	6 (4)	✔	N/A	✔	✔	✔
Abdominal Pain	N/A	✔	8.1 (4.5)	12 (#)	23 (#)	13-17 (11)
Nervous System						
Insomnia	0 (8)	N/A	✔	N/A	✔	6-7 (10)
Emotional Lability	6 (4)	N/A	N/A	N/A	N/A	N/A
Nervousness	✔	N/A	5.4 (1.6)	N/A	✔	2-3 (2)
Depression	✔	✔	5.8 (3.6)	5 (#)	11 (#)	5-11 (7)
Respiratory System						
URI (bronchitis)	15 (19)	N/A	N/A	21 (#)	N/A	9-11 (11)
Sinusitis	15 (10)	N/A	8.1 (9.7)	8 (#)	7 (#)	8-10 (7)
Skin and Appendages						
Rash	✔	✔	✔	✔	4 (#)	4-5 (2)
Alopecia	✔	✔	✔	✔	✔	✔
Nutritional						
Weight Change (+ or -)	9 (6)	✔	✔	✔	✔	✔
Urogenital System						
Breast Pain	17 (8)	✔	8.1 (5.3)	16 (#)	32 (#)	13-26 (9)
Vaginal Bleeding	11 (0)	✔	✔	9 (#)	3 (#)	2-6 (0)
Dysmenorrhea	✔	N/A	✔	8 (#)	13 (#)	3-6 (<1)
Metrorrhea	✔	✔	✔	N/A	✔	✔
Other						
Accidental Injury	17 (4)*	N/A	N/A	N/A	5 (#)	9-10 (9)
↓ Carbohydrate Tolerance	N/A	✔	N/A	✔	✔	✔

*Including one upper extremity fracture in each group
#Incidence for placebo not available
N/A Incidence not available
✔ Adverse event reported; specific percentages not available

Table 8. Common Adverse Events (%), by System, Reported for Transdermal Estrogen Combination[58]

Adverse Event	Combipatch
Body as a Whole	
Headache	18-20 (20)
Back Pain	9-11 (5)
Digestive System	
Nausea	8-11 (7)
Gastroenteritis (vomiting)	N/A
Abdominal Pain	6-7 (4)
Nervous System	
Insomnia	3-6 (7)
Emotional Lability	N/A
Nervousness	3-5 (1)
Depression	3-5 (9)
Respiratory System	
URI (bronchitis)	N/A
Sinusitis	4-9 (9)
Skin and Appendages	
Rash	N/A
Application site rxn.	2-6 (4)
D/C due to appl. site rxn.	N/A
Nutritional	
Weight Change (+ or -)	N/A
Urogenital System	
Breast Pain	25-31 (7)
Vaginal Bleeding	N/A
Dysmenorrhea	20-21 (5)
Metrorrhea	N/A
Other	
Accidental Injury	4-5 (8)
↓ Carbohydrate Tolerance	N/A

N/A Incidence not available

Dosing and Administration for the Estrogen Combination Products

Dosing for estrogen combination products are described in the following tables.

Table 10. Dosing for the Oral Estrogen Combination Products[52-57]

	Availability	Dose /Frequency/Duration
Activella (estradiol/nore-thindrone)	1mg estradiol / 0.5mg norethindrone per tablet, 28 tablet dial pack	One tablet QD.
Estratest (esterified estrogens/methyl-testosterone)	1.25mg esterified estrogens / 2.5mg methyltestosterone tablet	One tablet QD, given cyclically (3 weeks on and 1 week off).
Estratest H.S. (esterified estrogens/methyl-testosterone)	0.625mg esterified estrogens / 1.25mg methyltestosterone tablet	One tablet QD, given cyclically (3 weeks on and 1 week off).
FemHRT (ethinyl estradiol/nore-thindrone)	5 mcg ethinyl estradiol / 1mg norethindrone tablet, in bottles of 90 or blister cards of 28	One tablet QD, continuous.
Prefest Ortho-Prefest (17β-estradiol/norgestimate)	1mg estradiol pink tablets and 1mg estradiol/0.09mg norgestimate white tablets, supplied in a blister card with the following configuration: 3 pink tablets followed by 3 white tablets for a total of 30 tablets per card	One tablet QD continuously (pink tablet for 3 days, followed by white tablet for 3 days, repeated continuously).
Premphase** (conjugated estrogens / medroxyprogesterone)	0.625mg conj. estrogens (maroon tablet) / 0.625mg conj. estrogens / medroxyprogesterone 5mg (light blue tablet) Available as the 28-day EZ Dial dispenser.	One tablet QD* (maroon tablet on days 1-14 followed by the light blue tablet on days 15-28).
Prempro** (conjugated estrogens / medroxyprogesterone)	♦ 0.3mg conj. estrogens / 1.5mg medroxyprogesterone tablet ♦ 0.45mg conj. estrogens / 1.5mg medroxyprogesterone tablet ♦ 0.625mg conj. estrogens / 2.5mg medroxyprogesterone tablet ♦ 0.625mg conj. estrogens / 5mg medroxyprogesterone tablet All available as the 28-day EZ Dial dispenser.	One tablet QD*, starting with the 0.3mg/1.5mg dose and adjusting based on response.

*Only for women with significant risk of osteoporosis and non-estrogen medications must be carefully considered.

**When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.

Table 11. Dosing for Transdermal Estrogen Combination Product[58]

	Availability	Dose/Frequency/Duration
Combipatch (estradiol/nore-thindrone)	0.05mg estradiol/0.14mg norethindrone per day patch 0.05mg estradiol/0.25mg norethindrone per day patch	Continuous combined regimen: One patch applied twice weekly, worn continuously. Continuous sequential regimen: Combipatch is applied as a sequential regimen in combination with an estradiol-only delivery system. E.g.: A estrogen only patch is applied as appropriate for the first 14 days of a 28-day cycle, followed by Combipatch, applied twice weekly, for the remainder of the 14 days left in the cycle.

Comparative Effectiveness of the Estrogen Combination Products

Table 16 summarizes outcomes data from recently published trials, on the effects of estrogens on vasomotor symptoms, vaginal atrophy, and on the risks of treatment.

Table 13. Additional Outcomes Evidence for the Estrogen Combination Products

Study	Sample	Duration	Results
Women's HOPE[4]	n=241 postmenopausal women, mean age 54 years, with moderate-severe vasomotor symptoms	12 weeks	1) When given placebo, conjugated estrogens, or conjugated estrogen with medroxyprogesterone, the result on vasomotor symptoms was: ♦ A statistically significant ($p<0.001$) reduction from baseline (12-13 hot flashes/day), to post treatment (1-5 hot flashes/day), compared to placebo, was observed in the number and severity of symptoms. 2) The effect on vulvar and vaginal atrophy was: ♦ Vaginal maturation indexes at cycles 6 and 13 showed differences from placebo that were statistically significant ($p<0.001$) for both the estrogen and estrogen plus medroxyprogesterone group.
WHI[15]	n=16,608 predominantly healthy postmenopausal women, mean age 63 years, 84% white, 7% black and 6% Hispanic	5 years (average follow-up, stopped early)	For women randomized to Prempro versus placebo: ♦ Absolute excess risks per 10,000 person-years in the Prempro group were 7 more coronary heart disease events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers. ♦ Absolute risk reductions per 10,000 person-years were 6 fewer colorectal cancers and 5 fewer hip fractures. ♦ There was no difference in the groups in terms of all-cause mortality.
Transdermal vs. oral estrogen in smokers[64]	n=82 healthy postmenopausal smokers	6 months	The results of transdermal estrogen plus a progestin, oral estrogen plus a progestin, or placebo showed: ♦ Only the transdermal estrogen group showed more consistent reductions in total peripheral resistance at rest and in response to mental stress. ♦ Post-treatment concentrations of serum estradiol and estrone were lower and the serum estradiol/estrone ratio closer to pre-menopausal values in the transdermal estrogen group.

Conclusions

All estrogen / progestin combination products have been shown to be effective for the treatment of symptoms associated with menopause. There are no significant differences in drug interactions or adverse effects when comparing the same dosage forms. All brand estrogen combination products are comparable to each other and to the generics and offer no significant clinical advantage over other alternatives in general use.

Recommendations

No brand combination estrogen product is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
Anti-inflammatory Agents, Intranasal Corticosteroids (AHFS Class 520800)
March 24, 2004

I. Overview

Intranasal corticosteroids are the most effective medication class for the treatment of allergic rhinitis and may be useful for non-allergic rhinitis. These agents produce anti-inflammatory and vasoconstrictive effects on nasal mucosa through mechanisms which have not been totally elucidated. Allergic rhinitis is estimated to affect 10-30% of adults and up to 40% of children in the U.S.[1] The common symptoms of this chronic illness include runny nose, sneezing, itchy nose, and congestion. Less common symptoms may include headache, impaired smell and conjunctival symptoms. These symptoms can have a significant impact on quality of life for both adults and children, resulting in school absenteeism and decreased work productivity. Additionally, several comorbidities may exist with poorly controlled allergic rhinitis. These include worsening asthma, sinusitis, otitis media, sleep disorders (e.g., snoring and sleep apnea), pharyngitis, laryngitis, and conjunctivitis.[2]

The pathophysiology of allergic rhinitis involves a complex inflammatory response including both early- and late-phase responses. After exposure to an allergen, the early-phase response is thought to involve IgE molecules binding to mast cells in the nasal mucosa or circulating basophils, which then trigger the formation and release of chemical mediators (e.g., histamine, leukotrienes, bradykinin, etc.). Several hours after an immediate reaction, a late-phase response may be seen involving cellular infiltration (e.g., eosinophils, basophils, monocytes, lymphocytes) as well as release of chemical mediators such as histamine and leukotrienes.[2] Non-allergic rhinitis does not involve an IgE-mediated immune reaction, but can be difficult to distinguish from allergic rhinitis based on similar symptoms. Patients with nonallergic rhinitis tend to have less nasal itching and conjunctival irritation.

Treatment of allergic and non-allergic rhinitis includes trigger avoidance (e.g., pollens, dust mites, molds, etc.) and pharmacologic treatment with a wide variety of agents. Treatment options may target certain symptoms or the underlying inflammatory response. One of the most common options includes use of oral antihistamines; however, intranasal corticosteroids have improved efficacy in relieving the symptom of nasal congestion. Other options include intranasal antihistamines, oral decongestants, oral corticosteroids, intranasal cromolyn sodium, oral anti-leukotriene agents, and the intranasal anti-cholinergic, ipratropium bromide. Patients with very severe rhinitis may benefit from allergen immunotherapy. As will be discussed in the next section, intranasal corticosteroids are the most effective class for controlling symptoms of allergic rhinitis.[1] This review encompasses all dosage forms and strengths

Table 1. Intranasal Corticosteroids Included in this Review

Generic Name	Brand Name Example(s)
Beclomethasone dipropionate monohydrate	Beconase AQ®
Budesonide	Rhinocort Aqua™
Flunisolide	Nasalide®*, Nasarel®, generic
Fluticasone propionate	Flonase®
Mometasone furoate monohydrate	Nasonex®
Triamcinolone acetonide	Nasacort®*, Nasacort® AQ, Tri-Nasal®*

*Products currently not available

II. Current Treatment Guidelines

Diagnosis and Management of Rhinitis: Complete Guidelines of Joint Task Force on Practice Parameters in Allergy, Asthma and Immunology[1]

Practice parameters for the diagnosis and management of rhinitis were published in 1998 by a joint task force representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology. The guidelines address multiple different types of rhinitis, including allergic rhinitis, nonallergic rhinitis, occupational rhinitis, hormonal rhinitis, drug-induced rhinitis, and gustatory and food-related rhinitis.

Evaluation of the patient with rhinitis should include a detailed history of patterns or seasonal variations in symptoms, chronicity, medications taken and patient response, occupational or environmental factors that may contribute to precipitation of symptoms, and coexisting conditions.

The first step in managing rhinitis is avoidance of precipitating factors. These triggers may include allergens (e.g., dust mites, molds, pollens, pets, etc.), occupational or environmental irritants (e.g., chemicals), or medications that may contribute to rhinitis symptoms. Pharmacological therapy can then be instituted if required in accordance with the etiology and pattern of the patient's rhinitis symptoms (e.g., prophylactic medications initiated several weeks before the start of the anticipated onset of symptoms for seasonal allergic rhinitis). Intranasal steroids are the most effective drugs for controlling the symptoms of allergic rhinitis, including nasal congestion. They may be instituted without prior trials of oral antihistamines or decongestants, and should be tried prior to initiating any oral steroid therapy. Intranasal steroids may also be effective for some forms of nonallergic rhinitis. Oral antihistamines effectively relieve symptoms of itching, sneezing, rhinorrhea, and allergic conjunctivitis, but have little effect on nasal congestion; they are not generally useful for nonallergic rhinitis. Due to risks associated with sedation and performance impairment with first-generation antihistamines, the second-generation oral antihistamines are generally recommended if an oral antihistamine is selected for therapy.

Other treatment options include intranasal antihistamines, oral decongestants, nasal decongestant sprays, systemic corticosteroids, nasal cromolyn, and intranasal anticholinergics. Intranasal antihistamines may help with nasal congestion, but potential adverse effects of bitter taste and systemic absorption causing sedation may be observed. Oral decongestants are useful in relieving nasal congestion in allergic and non-allergic rhinitis. Potential adverse events with these agents include insomnia, loss of appetite, nervousness and increased blood pressure, which may limit their use in some patient groups. Nasal decongestant sprays should be limited to no more than three or four days due to the risk for rebound congestion with chronic use. Nasal cromolyn may be helpful for some patients with allergic rhinitis, but the four times daily dosing schedule may curb its use. Oral corticosteroids should be reserved for severe cases and used in short bursts in order to avoid HPA axis suppression. Intranasal anticholinergics (e.g., ipratropium bromide) are effective in relieving rhinorrhea, but are ineffective for other nasal symptoms. This drug may be especially helpful for elderly patients suffering from profuse, watery rhinorrhea.

Institute for Clinical Systems Improvement (ICSI) Health Care Guideline: Rhinitis[3]

This guideline was developed by a work group incorporating the fields of allergy, internal medicine and pharmacy to assist clinicians in the diagnosis and management of rhinitis. The following table is adapted from this guideline regarding medication options for the treatment of allergic rhinitis.

Table 2. Medications for the Treatment of Allergic Rhinitis

Medication	Symptom			
	Sneezing	**Runny nose**	**Itching**	**Congestion**
Intranasal steroids	+++	+++	+++	++
Antihistamines	+++	++	+++	±
Decongestants	-	-	-	+++
Cromolyn sodium	+	+	+	±
Anticholinergics	-	+++	-	-
Leukotriene receptor blockers				±

Key: - no effect ++ moderate effect
± negligible effect +++ pronounced effect
+ slight effect

For nonallergic rhinitis, this guideline recommends intranasal corticosteroids, oral decongestants, topical or oral antihistamines, or Breathe-Right strips as selections for symptomatic therapy.

Allergic Rhinitis and Its Impact on Asthma (ARIA)[4]

The ARIA initiative was developed by an independent expert group in collaboration with the World Health Organization and released in November 2001. One of the major differences with this guideline is the introduction of a new classification system for allergic rhinitis. The guideline proposes that allergic rhinitis be subdivided into intermittent or persistent categories, and then further classified according to severity of symptoms (mild or moderate/severe). After the appropriate diagnosis and classification of allergic rhinitis has been made, patients are treated in a step-wise approach, starting with allergen avoidance.

For patients with intermittent mild symptoms, recommended medications include oral antihistamines (second-generation agents if available), or nasal antihistamines, and/or oral decongestants. For patients with intermittent moderate/severe symptoms, recommended medications include those listed for patients with mild symptoms with additional drug therapy choices including nasal corticosteroids or cromolyn. The same medications are recommended for patients with persistent mild symptoms, with follow-up after 2-4 weeks. For those patients with persistent moderate/severe symptoms, the recommended initial therapy is with a nasal corticosteroid. For patients not responding to the nasal corticosteroid after 2-4 weeks, options include increasing the nasal corticosteroid dose, adding an oral antihistamine if symptoms of itching/sneezing are present, adding nasal ipratropium bromide if rhinorrhea is present, or adding decongestants or oral steroids if blockage continues. For all classifications of allergic rhinitis, if conjunctivitis is present, adding an oral antihistamine, ocular antihistamine or ocular cromolyn is recommended.

III. Indications

Table 3. FDA Approved Indications for Intranasal Corticosteroids [5-10]

Drug	Indications			
	Seasonal Allergic Rhinitis	**Perennial Allergic Rhinitis**	**Nonallergic (Vasomotor) Rhinitis**	**Other**
Beclomethasone dipropionate (adults & children ≥ 6 years)	√	√	√	√[1]
Budesonide (adults & children ≥6 years)	√	√		
Flunisolide (adults & children ≥6 years)	√	√		
Fluticasone propionate (adults & children ≥4 years)	√	√	√	
Mometasone furoate (adults & children ≥2 for treatment)	√ (adults & adolescents ≥12 for prophylaxis)	√		
Triamcinolone acetonide (adults & children ≥6 years)	√	√		

[1]Prevention or recurrence of nasal polyps following surgical removal

IV. Pharmacokinetics

Table 4. Pharmacokinetics of Intranasal Corticosteroids [5-10]

Drug	Pharmacokinetic Parameters				
	Bioavailability	**Metabolism**	**Metabolites**	**Excretion**	**$T_{1/2}$**
Beclomethasone dipropionate	44%*	Via esterase enzymes found in most tissues	Major, active: B-17-MP Minor, inactive: B-21-MP & BOH	Feces 60%, urine 12% (based on oral dosing)	0.5 hr – parent 2.7 hrs B-17-MP
Budesonide	34%	Liver – CYP3A	16α-hydroxyprednisolone & 6β-hydroxybudesonide	Urine (~ 2/3) & Feces (~1/3)	2-3 hrs
Flunisolide	50%**	Liver	6β-OH, glucornide & sulfate conjugates	Urine (~50%) & feces (~50%)	1-2 hrs
Fluticasone propionate	2%	Liver – CYP3A	17β-carboxylic acid	Feces (95%) & urine (5%)	7.8 hrs
Mometasone furoate	***	Liver – CYP3A	6β-hydroxy-mometasone furoate (minor)	Bile (majority) & urine (limited)	5.8 hrs
Triamcinolone acetonide	***	--	6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide, 21-carboxy-6β-hydroxytriamcinolone acetonide	--	3.1 hrs

*Of major active metabolite, B-17-MP; absorption of unchanged beclomethasone dipropionate reported as undetectable.
**Total absorption of the NASAREL formulation is 25% less than that of the NASALIDE formulation (products are not bioequivalent).
***Information not included in package labeling.

V. Drug Interactions [5-11]

In general, concerns regarding drug-drug interactions with the inhaled nasal corticosteroids are limited due to the method of administration and relatively low systemic bioavailability with most of these agents. Potential absorption into systemic circulation may occur through absorption in nasal mucosa as well as through the gastrointestinal tract from swallowing the inhaled drug.

There are no reported drug interactions for beclomethasone dipropionate, flunisolide, mometasone furoate, or triamcinolone acetonide. Due to metabolism in the liver via the cytochrome P450 3A isoenzymes, the potential for clinically significant drug-drug interactions exist with both budesonide and fluticasone propionate. Inhibitors of CYP3A isoenzymes may lead to reduced metabolism of these agents with potentially increased systemic exposure to the parent drug. The greatest concern with increased systemic effects of corticosteroids is the potential to induce hypercorticism and adrenal suppression.

Administration of oral ketoconazole to patients receiving oral budesonide resulted in significantly increased plasma concentrations of budesonide (~ seven fold increase). The manufacturer recommends caution when using concomitant drugs that are inhibitors of the CYP3A system (e.g., itraconazole, clarithromycin, erythromycin, etc.).

Fluticasone propionate is a substrate for CYP3A4 and has the potential for increased systemic effects when administered concomitantly with potent CYP3A4 inhibitors. Coadministration with ritonavir is not recommended due to significantly increased plasma fluticasone propionate levels with correlated significant decreases in plasma cortisol AUC (86% decrease). Coadministration with ketoconazole resulted in slight increases in fluticasone propionate plasma levels and a slight reduction in plasma cortisol AUC (7%). The manufacturer recommends caution when using potent CYP3A4 inhibitors such as ketoconazole concomitantly with fluticasone dipropionate.

VI. Adverse Drug Events [5-13, 24-25]

The most common side effects of nasally inhaled corticosteroids include local effects such as nasal irritation and bleeding. Nasal septal perforations have been reported rarely and patients should be instructed to direct sprays away from the nasal septum during administration.

Patients switched to a nasally inhaled corticosteroid from oral corticosteroid therapy should be closely monitored for signs of adrenal insufficiency and steroid withdrawal (e.g., joint/muscular pain, lassitude, depression, etc.). Conversely, excessive doses of intranasal corticosteroids may lead to systemic steroid effects (e.g., hypercorticism and adrenal suppression). To minimize the risk of systemic corticosteroid exposure, in general, intranasal steroid doses should be titrated to the lowest effective dose.

Localized *Candida albicans* infections of the nose and pharynx have been reported rarely in users of intranasal corticosteroids. Patients receiving steroid therapy may be more susceptible to infections and should be used with caution, if at all, in those with active or quiescent tuberculosis infection, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

While it is recommended to monitor pediatric patients taking intranasal corticosteroids for reduced growth velocity based on reports of beclomethasone nasal spray slowing growth in children, other studies have not demonstrated effects on growth.[12-13, 24-25]

All intranasal corticosteroids are classified as Pregnancy Category C due to the development of teratogenic and fetotoxic effects in animal models. These drugs should not be used during pregnancy unless the potential benefit to the mother outweighs the risks of use to the fetus.

Table 5 includes adverse events reported in each product's respective package labeling.

Table 5. Adverse Drug Event Comparison[5-9, 10, 14, 15*]

Adverse Event	Beconase AQ	Flonase (100mcg)	Flonase (200mcg)	Nasacort	Nasacort (220mcg)	Nasacort AQ (220mcg)	Nasalide	Nasarel	Nasonex (100mcg)	Nasonex (200mcg)	Rhinocort AQ
Asthma symptoms	-	7.2%	3.3%	-	-	-	-	-	-	-	-
Bronchospasm	-	-	-	-	-	-	-	-	-	-	2.0%
Congestion	-	-	-	< 5.0%	-	-	-	-	-	-	-
Coughing	-	3.6%	3.8%	-	9.4%	-	-	-	13.0%	7.0%	2.0%
Dry mucous membranes	-	-	-	< 5.0%	-	-	-	-	-	-	-
Dysmenorrhea	-	-	-	-	-	-	-	-	1.0%	5.0%	-
Dyspepsia	-	-	-	-	4.7%	-	-	-	-	-	-
Epistaxis	-	6.0%	6.9%	< 5.0%	11.0%	2.7%	≤ 5.0%	3.0-9.0%	-	-	8.0%
Epistaxis/blood-tinged mucous	-	-	-	-	-	-	-	-	8.0%	11.0%	-
Fever	-	-	-	-	7.9%	-	-	-	-	-	-
Headache	-	6.6%	16.1%	18.0%	-	-	≤ 5.0%	-	17.0%	26.0%	-
Headache, nausea, lightheadedness	< 5.0%	-	-	-	-	-	-	-	-	-	-
Increased cough	-	-	-	-	-	2.1%	-	1.0-3.0%	-	-	-
Mild nasopharyngeal irritation	24.0%	-	-	-	-	-	-	-	-	-	-
Musculoskeletal pain	-	-	-	-	-	-	-	-	1.0%	5.0%	-
Nasal burning and stinging	-	2.4%	3.2%	-	-	-	45.0%	13.0%	-	-	-
Nasal congestion	-	-	-	-	-	-	≤ 5.0%	-	-	-	-
Nasal dryness	-	-	-	-	-	-	-	1.0-3.0%	-	-	-
Nasal irritation	-	-	-	2.8%	-	-	-	-	-	-	2.0%
Nasal stuffiness, epistaxis, rhinorrhea, tearing eyes	< 3.0%	-	-	-	-	-	-	-	-	-	-
Nausea	-	-	-	-	6.3%	-	≤ 5.0%	1.0-3.0%	5.0%	1.0%	-
Nausea/vomiting	-	4.8%	2.6%	-	-	-	-	-	-	-	-
Otitis	-	-	-	-	4.7%	-	-	-	-	-	-
Pharyngitis	-	6.0%	7.8%	-	-	5.1%	-	1.0-3.0%	10.0%	12.0%	4.0%
Sinusitis	-	-	-	-	-	-	-	-	4.0%	5.0%	-
Sneezing	-	-	-	< 5.0%	-	-	≤ 5.0%	-	-	-	-
Sneezing attacks immediately following administration	4.0%	-	-	-	-	-	-	-	-	-	-
Sore throat	-	-	-	-	-	-	≤ 5.0%	-	-	-	-
Throat discomfort	-	-	-	< 5.0%	5.5%	-	-	-	-	-	-
Transient aftertaste	-	-	-	-	-	-	-	17.0%	-	-	-
URI	-	-	-	-	-	-	-	-	5.0%	6.0%	-
Viral Infection	-	-	-	-	-	-	-	-	8.0%	14.0%	-
Watery eyes	-	-	-	-	-	-	≤ 5.0%	-	-	-	-

*Refer to package labeling for placebo adverse event rates

Nasonex 200mcg related ADE's in adults and children ≥ 12 years of age; Nasonex 100mcg related ADE's for children 3-11 years of age

Nasacort 220mcg related ADE's in children 3-11 years of age

Nasacort AQ 220mcg related ADE's in adults and children ≥ 12 years of age

VII. Dosing and Administration [5-10]

Table 6 includes the recommended daily dose for different age groups.

Table 6. Intranasal Corticosteroid Comparative Dosing

Drug	***Dosing & Administration***		
	Age group	**# Nasal Inhalations**	**Total daily dose**
Beclomethasone dipropionate	≥12 years old	1 or 2 inhalations in each nostril twice a day	168 – 336 mcg
	6 – 11 years old	1 inhalation in each nostril twice a day[1]	168 mcg*
Budesonide	***Starting dose:***		
	≥6 years old	1 spray per nostril once daily	64 mcg
	Maximum dose:		
	≥12 years old	4 sprays per nostril once daily	256 mcg
	6 – 11 years old	2 sprays per nostril once daily	128 mcg
Flunisolide	***Starting dose:***		
	≥14 years old	2 sprays in each nostril twice a day	232 mcg (Nasarel) 200 mcg (Nasalide)
	6-13 years old	1 spray in each nostril three times a day ***or*** 2 sprays in each nostril twice a day	174 – 232 mcg (Nasarel) 150 – 200 mcg (Nasalide)
	Maximum dose:		
	≥14 years old	8 sprays in each nostril per day	464 mcg (Nasarel) 400 mcg (Nasalide)
	6 – 13 years old	4 sprays in each nostril per day	232 mcg (Nasarel) 200 mcg (Nasalide)
Fluticasone propionate	***Starting dose:***		
	Adults	2 sprays in each nostril once daily	200 mcg
	≥4 to adult	1 spray in each nostril once daily	100 mcg
	Maximum dose:	2 sprays in each nostril once daily	200 mcg
	Once symptoms are adequately controlled, reduce dosage to 1 spray in each nostril daily.		

Drug	*Dosing & Administration*		
	Age group	**# Nasal Inhalations**	**Total daily dose**
Mometasone furoate	>12 years old	2 sprays in each nostril once daily	200 mcg
	2 – 11 years old	1 spray in each nostril once daily	100 mcg
Triamcinolone acetonide	***Starting dose:***		
	>12 years old	2 sprays in each nostril once daily	220 mcg
	6 – 11 years old	1 spray in each nostril once daily	110 mcg
	Maximum dose:	2 sprays in each nostril once daily	220 mcg

[*]Dosage may be increased up to 2 inhalations in each nostril twice daily for children with inadequate response or severe symptoms, but dosage should be reduced back to 1 inhalation in each nostril twice a day once adequate control is achieved.

VIII. Effectiveness

The New England Medical Center Evidence-based Practice Center prepared an evidence report/technology assessment on the management of allergic and nonallergic rhinitis for the Agency on Healthcare Research and Quality that was published in May 2002.[16] Experts systematically reviewed published literature to address key issues and questions in the management of allergic and nonallergic rhinitis. Studies evaluating intranasal steroids were an important part of this review.

Nonallergic Rhinitis (NAR)

In the 2002 AHRQ evidence report, three trials evaluated the efficacy of intranasal steroids versus placebo or ipratropium bromide in the treatment of NAR. The studies ranged in duration from 40 days to 12 weeks. One study evaluated two doses of budesonide versus placebo, while the other two studies compared ipratropium with either budesonide or beclomethasone.

The first study was a 12 week, randomized, double-blind, cross-over, placebo-controlled study comparing budesonide doses. Budesonide doses of 400 mcg and 800 mcg significantly improved the symptom of nasal obstruction in patients with at least 12 months of perennial rhinitis (n=59). No differences in efficacy were noted between the two doses and no significant side effects were reported. The second study evaluated only 14 patients with predominant symptoms of excessive nasal secretions in a non-randomized open label trial comparing ipratropium bromide with budesonide. Budesonide showed superior efficacy for nasal secretions and sneezing compared to ipratropium. However, a double-blind, randomized crossover trial comparing ipratropium 160 mcg vs. beclomethasone 400 mcg in 24 patients found no difference between the two drugs in terms of nasal symptom improvement.[16]

Mometasone furoate nasal spray was compared to placebo in a phase III, randomized, double-blind trial involving 329 patients. Patients receiving mometasone furoate for six weeks had an overall improvement rate of 56% compared to 49% for the placebo group. Improvement in the total nasal score by the investigator was greater for the mometasone furoate treatment group as compared to placebo, but the difference was not significant (p=0.09). There were no statistically significant differences in side effects between the two groups.[17]

A recent study compared intranasal fluticasone propionate with placebo in patients with NAR or non-allergic rhinitis with eosinophilic syndrome(NARES). Data from 983 patients $\geq$12 years old from three double-blind, randomized, placebo-controlled studies were evaluated. Patients received either 200 mcg or 400 mcg of fluticasone propionate or placebo. Efficacy was evaluated by change in total nasal symptom

score (including nasal obstruction, postnasal drip and rhinorrhea). Treatment with fluticasone propionate significantly improved total nasal symptom scores as compared to placebo ($p \leq 0.002$).[18]

A 12 week trial compared two dosing regimens of beclomethasone dipropionate in 112 patients. Patients with allergic or nonallergic rhinitis received a total of 400 mcg/day of beclomethasone dipropionate given either once daily or divided into two doses. Both dosing regimens had a similar efficacy for nasal symptoms and adverse event profiles.[19]

Beclomethasone dipropionate & fluticasone propionate are approved for the treatment of non-allergic rhinitis (NAR). One formulation of budesonide (Rhinocort) was also approved for this indication, but has been replaced with the aqueous formulation (Rhinocort Aqua), which does not have an approved indication for NAR.

Allergic Rhinitis

A meta-analysis of randomized, controlled trials (n=17) comparing intranasal steroids and oral antihistamines for the treatment of seasonal or perennial allergic rhinitis showed an overwhelming advantage for the inhaled nasal steroids for nasal symptom relief as compared to the oral antihistamines. Symptom improvement was seen in nasal blockage, discharge, sneezing, itching and postnasal drainage. The most commonly reported adverse events from nasal steroids were epistaxis, headache and pharyngitis. None of the studies reported systemic side effects from the intranasal steroids.[20]

The superiority of symptom relief with intranasal steroids as compared to oral antihistamines was confirmed by another meta-analysis as well as the 2002 AHRQ evidence report.[16,21]

No specific intranasal steroid has been found to be superior to the others in this class of drugs. All are efficacious and safe.[2] Selection of an intranasal steroid will rely mainly on product attributes such as dosing frequency and patient preference due to smell or taste of the product. Several studies have been conducted to evaluate differences in patient preferences based on sensory attributes. Stanaland reviewed studies comparing triamcinolone acetonide, fluticasone propionate and mometasone furoate and budesonide versus fluticasone propionate. In the first study, triamcinolone acetonide was rated by patients as having less odor, better comfort during administration and less runoff than mometasone furoate, less runoff and odor strength compared to fluticasone propionate, and producing less aftertaste and irritation than either mometasone furoate or fluticasone propionate. Patients expressed an overall preference for triamcinolone acetonide. In the study comparing budesonide versus fluticasone, budesonide was preferred 3:2 over fluticasone by patients due to attributes such as less forceful spray, less smell, taste, aftertaste, and rundown into the throat. A third study was reviewed as well that compares budesonide to fluticasone. No differences in efficacy were noted, but patients receiving budesonide reported greater improvements in quality of life.

A trial was conducted comparing once-daily triamcinolone acetonide with twice-daily beclomethasone dipropionate for seasonal allergic rhinitis in 152 patients. Both treatments showed efficacy in relieving the symptoms of allergic rhinitis with no significant differences between the two regimens. However, patients reported improved taste and smell with triamcinolone acetonide as compared to beclomethasone dipropionate ($p \leq 0.05$).[22]

Prevention of nasal polyps following surgical removal

Nasal steroids can reduce the size of nasal polyps and increase nasal airway patency. Several intranasal steroids, including betamethasone and budesonide, have proven efficacious in the treatment of nasal polyposis.[23] The only intranasal steroid currently with an FDA approved indication for nasal polyposis is beclomethasone.

IX. Conclusions

Selecting specific agents within a drug class relies largely on drug efficacy, safety and adverse event profile.

Efficacy

Within the intranasal corticosteroid drug class, no single agent stands out as being more efficacious than the other agents within the class. In terms of FDA approved indications, only two are approved for treatment of nonallergic rhinitis: beclomethasone dipropionate and fluticasone propionate. All intranasal steroids have approved indications for seasonal and perennial allergic rhinitis. The only agent with an FDA-approved indication for nasal polyposis is beclomethasone.

Safety & Adverse Events

Fluticasone propionate and mometasone furoate both have reportedly low bioavailability (<2%) which may reduce the chances of systemic side effects, though studies typically don't report symptoms of systemic side effects for any of the intranasal steroids. Budesonide & fluticasone propionate have the potential for drug-drug interactions based on CYP3A metabolism. The most common side effects of all nasal steroids are nasal irritation and bleeding, but differences among the agents with regard to this adverse event have not been demonstrated.

Availability

Production of Nasalide® (flunisolide) was discontinued in the spring of 2003 per communication with IVAX Pharmaceuticals. In a "Dear Healthcare Professional" letter from IVAX dated March 31, 2003, it was noted that Nasalide® was discontinued voluntarily and being replaced with Nasarel® based on an improved formulation leading to less stinging and burning as compared to Nasalide®. Per that communication, the last lot of Nasalide® will expire in June 2004.

Production of Nasacort ®(triamcinolone acetonide) was also voluntarily discontinued as of July 24, 2003 per communication with Aventis Pharmaceuticals. The product has been replaced with Nasacort® AQ in accordance with Title VI of the Clean Air Act that requests removal of CFCs as the vehicle delivery system. Another formulation of triamcinolone, Tri-Nasal®, has been discontinued, though attempts to discuss with the manufacturer were unsuccessful.

These three products may still be in circulation, but the companies are unable to give an estimation of how much supply is left in circulation. Starting new patients on one of these products for a chronic condition would not be ideal given the fact that it is unclear when the supply would run out and would require the patient to switch therapies. IVAX Pharmaceuticals was the only company able to provide an expiration date for the last manufactured lot of Nasalide®. Clearly, because the discontinuation of Nasalide® was based on a high incidence of burning and stinging on administration, as well as the fact that it will be expired within 4 months, this drug is not a recommended agent for use. It appears from package insert data that Nasacort® has a greater incidence of adverse events than Nasacort® AQ, but since they were not head-to-head trials, this may not be completely accurate.

All brand products within the class reviewed are comparable to each other and to generics in this class and offer no significant clinical advantage over other alternatives in general use. Additionally, Nasalide® possesses an extensive adverse effect profile.

X. Recommendations

No brand intranasal corticosteroid is recommended for preferred status and Nasalide® should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency

Pharmacy and Therapeutics Committee Meeting

Pharmacotherapy Review of Respiratory Products

March 24, 2004

Overview

Asthma

It is estimated that 14 to 15 million people in the United States have asthma. Asthma is the cause of more than 100 million days of restricted activity and 470,000 hospitalizations per year. More than 5,000 people die secondary to asthma complications each year.[1] There have been many advances made in the understanding of the disease, particularly the recognition of asthma as an inflammatory disorder, which have led to the availability of improved medications. Despite these advances, the morbidity and mortality rates have continued to rise.[2,3] Many reasons have been hypothesized including noncompliance, poor follow-up, and the underutilization of corticosteroid therapy.[2] In an effort to address this growing problem, the National Institutes of Health (NIH) released the Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (EPR-2).[1]

Healthcare providers have an important opportunity to impact the management of asthma patients. In addition to the specific pharmacologic issues that will be addressed, there are other components of asthma management including patient education and environmental control. From the time a patient is diagnosed with asthma, the healthcare provider should teach basic facts about asthma, necessary medication skills (i.e., proper inhaler technique) and self-monitoring skills. Healthcare providers should also identify, through patient history or skin testing, possible irritants, allergens, or drugs to which the patient is sensitive. Table 1 contains a list of these examples, as well as other factors that can influence asthma severity. Because viral respiratory infections can influence asthma severity, annual influenza vaccines are recommended in patients with persistent asthma symptoms. Healthcare providers and patients can work together to incorporate this information and develop a written, daily self-management plan.[1] Through this partnership effort and appropriate pharmacologic therapy, successful management of asthma will hopefully be achieved.

Table 1: Factors that may increase asthma symptoms[1]

Inhalant allergens	Irritants	Drugs	Other factors
Animal allergens House-dust mites Cockroach	Tobacco smoke Indoor and outdoor pollution	Aspirin NSAIDs Beta blockers	Rhinitis/sinusitis Gastroesophageal reflux

allergens Indoor fungi (molds) Outdoor allergens	Occupational exposures		Viral respiratory infections

Chronic Obstructive Pulmonary Disease (COPD)

COPD affects approximately 15 million Americans, and is the fourth leading cause of death in the United States.[3] Most notably, it is the only leading cause of death other than congestive heart failure that is increasing in prevalence, with white women having the highest increase in deaths.

There are four subsets of COPD, including chronic bronchitis, emphysema, peripheral airway disease, and asthmatic bronchitis. Chronic bronchitis involves chronic or recurrent excess mucus secretion with cough. These patients may have an associated asthmatic bronchitis, which implies some reversibility to the disorder. Emphysema is characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by destruction of their walls, yet without obvious fibrosis. Lung damage produced by smoking begins in the small airways; by the time obstruction is detected with pulmonary function tests, extensive damage has already occurred. Finally, peripheral airway disease includes inflammation of the terminal and respiratory bronchioles, fibrosis with narrowing of airway walls, and goblet cell metaplasia of the bronchiolar epithelium. Peripheral airway disease is a major component of both chronic bronchitis and emphysema, contributing to obstruction.

Major risk factors for COPD are smoking, age, male gender, existing impaired lung function, occupation, and α_1-antitrypsin deficiency. Less significant risk factors include air pollution, alcohol, race, nutritional status, family history, socioeconomic status, respiratory tract infections, and bronchial reactivity.

Evidence Based Medicine and Current Treatment Guidelines

Asthma

The first national guidelines for asthma were published in 1991, a second in 1997, and most recently have been updated in 2002.[1,4] The guidelines provide four components of effective asthma management:

- **Use of objective measures of lung function to assess the severity of asthma and to monitor the course of therapy**
- **Environmental control measures to avoid or eliminate factors that contribute to asthma severity**
- **Comprehensive pharmacologic therapy for long-term management designed to reverse and prevent the airway inflammation characteristic of asthma, as well as pharmacologic therapy to manage asthma exacerbations**

- **Patient education that fosters a partnership among the patient, his or her family, and clinicians**

For both adults and children, inhaled corticosteroids are recommended as preferred therapy in three of the four asthma classifications; mild persistent, moderate persistent, and severe persistent.[4]

The 2002 update addresses specific questions to help refocus clinical practice. These include the use of inhaled corticosteroids in children compared to other therapies, the safety of inhaled corticosteroids in children, and the use of combination therapy in both adults and children. (See Appendices 1 and 2 for treatment algorithms).[1]

COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines are the most referenced COPD guidelines worldwide. The guidelines are backed internationally by the National Heart, Lung, and Blood Institute and the World Health Organization. In July 2003, the committee issued updated guidelines that stress management plans for COPD that include: 1) Assess and monitor the disease, 2) reduce risk factors, 3) manage stable COPD, and 4) manage exacerbations.[5] The goals of any COPD care management plan should be to:

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat complications
- Prevent and treat exacerbations
- Reduce mortality

The care management plan should include management of stable COPD and exacerbations, with focus on pharmacological and non-pharmacological treatments. Tables 2 and 3 further describe components to managing stable and exacerbations of COPD.

Table 2. Management of Stable COPD[5]

Key Points
1) The overall approach should be characterized by a stepwise increase in treatment, depending on the severity of disease.
2) Health education can play a role in improving skills, ability to cope with illness, and health status.
3) Since none of the medications for COPD has been shown to modify long-term decline in lung function, the hallmark of the disease, pharmacotherapy is used to decrease symptoms and complications.
4) Bronchodilator medications are central to the symptomatic management of COPD and are given on an as-needed or regular basis to prevent or reduce symptoms.
5) Regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.
6) Addition of regular treatment with inhaled glucocorticosteroids to bronchodilator treatment is appropriate for symptomatic COPD patients with a FEV1 <50% of predicted and with repeated exacerbations.
7) Chronic treatment with systemic glucocorticosteroids should be avoided because of an unfavorable benefit-to-risk ratio.
8) All COPD patients benefit from exercise training programs, improving with respect to both exercise tolerance and symptoms of dyspnea and fatigue.
9) Long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.

Table 3. Management of COPD Exacerbations[5]

Key Points
1) Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.
2) The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified.
3) Inhaled bronchodilators (particularly inhaled beta-2 agonists and / or anticholinergics), theophylline, and systemic, preferably oral, glucocorticosteroids are effective treatments for exacerbations of COPD.
4) Patients with COPD exacerbations with clinical signs of airway infection (e.g., increased volume and change of color of sputum, and / or fever) may benefit from antibiotic treatment.
5) Noninvasive intermittent positive pressure ventilation (NIPPV) in exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay.

Appendix 3 includes the recommendations from GOLD guidelines can be used to stage patients with COPD, based on symptom characteristics, and provides pharmacotherapy recommendations for each stage.

Comparative Indications

Table 4 lists the product included in this review. This review encompasses all dosage forms and strengths.

Table 4. Antimuscarinic/Antispasmodic Product in this Review

Generic Name	Example Brand Names (s)	Formulation
Ipratropium	Atrovent	Aerosol
		Inhalation solution*

*Indicates generic available

Table 5 includes indications for its use.

Table 5. Ipratropium Indications [6]

Generic Name	Brand Name Example	Indications
Ipratropium	Atrovent	As a bronchodilator for maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

Pharmacokinetics

Table 6. Ipratropium Pharmacokinetics[7]

Agent	Absorption	Protein Binding	Metabolism Site	Half-life
Ipratropium	2% of 500mcg inhalation solution 20% of 36mcg inhalation aerosol	< 9%	Partially metabolized in liver	1.6 hours

Drug Interactions [7,8]

There are no clinically significant drug interactions with ipratropium. However, since ipratropium is minimally absorbed, there is a small potential for an additive interaction with concomitantly used anticholinergic medications. Thus, caution should be used in the co-administration of the combination treatment with other anticholinergic drugs.

Adverse Drug Events[7]

Table 7 lists reported adverse drug events for ipratropium inhalation aerosol and solution.

Table 7. Ipratropium Inhalation Aerosol and Solution Adverse Drug Events (%)*

Adverse Reaction	Inhalation aerosol	Inhalation solution (500 mcg tid) (n= 219)
CNS	-	-
Dizziness	1.0-3.0	2.3
Insomnia	-	0.9
Tremor	-	0.9
Nervousness	3.1	0.5
GI	-	-
Mouth dryness	1.0-3.0	3.2
Nausea	1.0-2.8	4.1
Constipation	< 1.0	0.9
GI Distress	1.0-3.0	-
Respiratory (lower)	-	-
Coughing	3.0-5.9	4.6
Dyspnea	-	9.6
Bronchitis	-	14.6
Bronchospasm	-	2.3
Sputum increased	-	1.4
Respiratory disorder	-	0
Respiratory (upper)	-	-
Upper respiratory tract infection	-	13.2
Pharyngitis	-	3.7
Rhinitis	-	2.3
Sinusitis	-	2.3
Miscellaneous	-	-
Headache	1.0-3.0	6.4
Pain	-	4.1
Influenza-like symptoms	-	3.7
Back pain	-	3.2
Chest pain	-	3.2
Hypertension/Hypertension aggravated	-	0.9
Arthritis	-	0.9
Dryness of oropharynx	5.0	-
Irritation	1.6-3.0	-
Symptom exacerbation	1.0-3.0	-
Palpitations	1.8	-
Rash	1.2	-

[*]Data are pooled from separate studies and are not necessarily comparable.

Dosing and Administration[7]

INHALATION AEROSOL

The usual dose is 2 inhalations (36 mcg) 4 times a day. Patients may take additional inhalations as required; however, do not exceed 12 inhalations in 24 hours.

INHALATION SOLUTION

The usual dose is 500 mcg (1 unit dose vial) administered 3 to 4 times a day by oral nebulization, with doses 6 to 8 hours apart. The solution can be mixed in the nebulizer with albuterol if used within 1 hour.

Effectiveness [1,5]

There are no head-to-head trials comparing ipratropium inhalation aerosol to solution in general use.

The asthma guidelines recommend antimuscarinic/antispasmodic as alternative therapy for patients who do not tolerate $beta_2$-agonist therapy. These agents may also provide some additive benefit to inhaled $beta_2$-agonist in severe exacerbations. They also recommend nebulized antimuscarinic/antispasmodic therapy be reserved for patients who can not use a MDI or in moderate-to-severe exacerbations.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends bronchodilators as central to symptom management. It also comments that all bronchodilators have a flat dose-response relationship for FEV_1 and recommends bronchodilator selection be based on availability and individual response to symptom relief and side effects. When considering route of administration (i.e., nebulizer vs. inhaler), these guidelines also state that nebulized treatment appears to provide subjective benefit in acute episodes, however, is not appropriate in the stabilized patient unless it has been shown to be more effective than conventional dose therapy.

Conclusion

In general use, the ipratropium MDI dosage formulation is recommended over the nebulizer treatment. Additionally, this product is only available in a brand formulation. Therefore, Atrovent offers a significant clinical advantage in general use over the other brands and generics.

Recommendation

The recommended product Atrovent be preferred.

Comparative Indications

Table 8 lists the product included in this review. This review encompasses all dosage forms and strengths.

Table 8. Corticosteroid Inhalers in this Review*

Generic Name	Brand Name Example(s)	Dosage Form
Beclomethasone	Qvar	MDI
Budesonide	Pulmicort Pulmicort Respules	Dry Powder Breath Activated Device Inhalation Suspension for nebulization
Flunisolide	Aerobid Aerobid-M	MDI MDI
Fluticasone	Flovent Flovent Rotadisk	MDI Dry powder inhaler
Triamcinolone	Azmacort	MDI

MDI - Metered dose aerosol inhaler
*No products currently available in generic formulations

All of the inhaled corticosteroids are indicated for patients with chronic asthma, although there are some age differences among the products:[9-14]

Aerobid ≥ 6 years old
Azmacort ≥ 6 years old
Flovent via Rotadisk, ≥ 4 years old; via MDI, ≥ 12 years old
Pulmicort via Turbuhaler, ≥ 6 years old; via Respules, 12 months to 8 years old
Qvar≥ 5 years old

None of these agents are indicated for the relief of acute bronchospasm.

Pharmacokinetics

As summarized in Table 9, the inhaled corticosteroids have similar pharmacokinetics. They do differ in terms of potency, as shown in Table 10. Potency is not correlated to efficacy, although the more potent agents may improve patient adherence because less drug is needed to achieve a similar effect.

Table 9. Comparative Pharmacokinetics of Inhaled Corticosteroids[9-14]

	Qvar (Beclomethasone)	Pulmicort (Budesonide)	Aerobid (Flunisolide)	Flovent (Fluticasone)	Azmacort (Triamcinolone)
Absorption Systemic bioavailability from lungs	≈ 20%	25%	40%	20%	21.5%
Distribution Volume of distribution (L/kg)	NA	4.3	1.8	3.5	1.4
Protein binding	87%	85% to 90%	NA	91%	≈ 68%
Metabolism Site	Liver (CYP3A)	Liver (CYP3A)	Liver	Liver (CYP3A)	Mostly from liver, less extensively from kidneys
Excretion Site	Feces, urine (< 10%)	Urine (≈ 60%), feces	Renal (50%); feces (40%)	Feces, urine (< 0.02%)	Urine (≈ 40%), feces (≈ 60%)
Half-life (hrs)	2.8	2.8	≈ 1.8	3.1	1.5

Table 10. Comparative Topical Potencies of Inhaled Corticosteroids[4]

Inhaled Corticosteroids	Topical Potency (skin test)*
Aerobid	330
Azmacort	330
Qvar	600
Pulmicort	980
Flovent	1200

*Numbers assigned in reference to dexamethasone, which has a value of "1" in the MacKenie Test

Drug Interactions[8,11]

While there are no significant drug interactions with inhaled corticosteroids, a placebo-controlled, crossover study in 8 healthy volunteers using fluticasone 1000mcg with multiple doses of ketoconazole resulted in increased fluticasone concentrations, a reduction in plasma cortisol AUC, and no effect on urinary cortisol excretion. Fluticasone is a substrate of cytochrome P450 3A4 and care should be exercised when fluticasone is administered with ketoconazole.

Adverse Drug Events [9-14]

Overall the inhaled corticosteroids are well tolerated. Comparison of most commonly observed adverse effects are summarized in Table 11. Some of the respiratory-tract related effects are related to drug administration. Symptoms such as cough and dysphonia will abate after 10 to 30 minutes. Upper respiratory tract infections and headache occur most frequently across the different drugs.

Table 11. Comparative Adverse Events (%) of Inhaled Corticosteroids[9-14]

Events	Aerobid	Azmacort	Flovent (MDI)	Flovent (powder)	Pulmicort (powder)	Pulmicort (solution)	Qvar
Respiratory System	25	--	15-22	16-22	19-24	34-38	9
Upper RTI	1-3	7-25	10-14	6-13	5-10	--	8
Pharyngitis	3-9	--	1-3	2-9	--	7-12	6
Rhinitis	3-9	2-9	3-6	4-6	2-11	--	3
Sinusitis	15	--	8-16	4-7	--	--	5-6
Nasal Congestion	3-9	--	--	--	--	5-9	1-3
Coughing	--	--	3-8	<1-6	--	1-3	1-3
Dysphonia							
Gastrointestinal	25	--	1-3	--	1-3	--	1
Nausea	1-3	--	1-3	--	1-4	--	--
Dyspepsia	3-9	1-3	2-5	3-11	2-4	--	--
Oral candidiasis	25	1-3	1-3	--	1-3	2-4	--
Vomiting	10	1-3	1-3	<4	--	2-4	<2
Diarrhea	3-9	1-3	--	1-3	1-3	2-3	--
Abdominal pain							
Miscellaneous	25	7-21	17-22	9-15	13-14	--	12
Headache	10	--	--	--	1-3	--	<2
Taste alternation	10	2-5	3-8	3-4	6-14	1-3	--
Influenza-like	--	--	--	--	--	3-5	5-8
syndrome	--	--	--	1-3	--	9-12	--
Viral infection							
Otitis media							

MDI – metered dose aerosol inhaler, RTI – respiratory tract infection

With more potent inhaled corticosteroids, especially fluticasone and budesonide, improved delivery systems, and guideline recommendations to use high doses, much attention has been focused on increased potential for systemic adverse effects of these agents. In a review and meta-analysis published in 1999, Lipworth reported that while effects on skin (i.e., bruising), and eyes (i.e., posterior subcapsular cataracts) are less with inhaled than oral corticosteroids, because of interindividual differences some patients may be more susceptible to these events, whatever agent they are using. [4,15]

The effects of the inhaled corticosteroids on adrenal suppression are less than that measured from oral corticosteroids. Fluticasone demonstrated a greater degree of adrenal suppression compared to beclomethasone, budesonide, and triamcinolone. [15] Again, interindividual susceptibilities may make some people more sensitive to the HPA axis effects of these agents. [4]

The potential negative effects of inhaled corticosteroids on growth in children are confounded by the effects of chronic asthma. Children with uncontrolled asthma may have a delay in prepubertal growth spurt as well as a delay in puberty that affects the associated pubertal growth spurt. When inhaled corticosteroids were compared to oral corticosteroids, there were lesser but measurable effects on lower-leg growth. When beclomethasone was compared to salmeterol and to theophylline, in both studies, the inhaled corticosteroid showed a negative effect on height velocity that was not demonstrated with the comparator agents. [15]

One long-term study followed the effects of an inhaled corticosteroid (budesonide via MDI) on asthmatic children who had a 1- to 2-year washout period from corticosteroid exposure. Compared to 18 patients with asthma who acted as controls and 51 healthy siblings of the children in the budesonide-treated group, 142 patients who were followed for a mean of 9.2 years were able to achieve normal adult height. There was no evidence of a dose-response relationship between the mean daily dose, the duration of treatment, or the difference between measured and target adult heights. [16]

Overall, the consensus is that controlling asthma in children with inhaled corticosteroids outweighs any negative effects on growth. [4,15]
The potential effects of inhaled corticosteroids on bone metabolism are also important, as the risk of osteoporosis for those on long-term oral corticosteroids is well documented. This area is not as well studied, although there is documentation of effects of the inhaled agents on biochemical bone markers. [15] Suissa et al recently reported on the effects on long-term (4 years) inhaled corticosteroids on risk of fracture in older patients (mean age 81 years). The rate of fracture was increased in the 5% of patients taking high doses (> 1000 mcg per day in beclomethasone equivalence units). [17]

Dosing and Administration

Comparative dosage recommendations for the inhaled corticosteroids for adults and children with asthma are listed in Tables 12 and 13, respectively. These are based on the 2002 updated asthma guidelines, dividing suggested doses into low, medium, and high. At each level of dosing, maximal effects may not be seen for several months. Guidelines do not recommend one inhaled corticosteroid over another. [4]

Whether using inhaled corticosteroids for asthma or COPD, when changing a patient from systemic corticosteroids to inhaled, it is important to have an overlap. Thus, the inhaled agent is employed for at least one week before the gradual decrease of the oral dose is started. Changes are made at 1 to 2 week intervals, with decrements not exceeding 2.5 mg prednisone or equivalent. Patients should be observed for signs of steroid withdrawal. If adrenal insufficiency occurs, the oral dose should be increased and the withdrawal process continued at a slower rate. [9-14]

Different dosage forms are available for these agents. The traditional metered aerosol dose inhaler (MDI) is provided with Qvar, Aerobid, Azmacort, and Flovent. Pulmicort is available in a dry powder that is in a breath-activated device. Flovent also has a dry powder device called a

Rotadisk. Finally, Pulmicort is also available as a suspension for inhalation, approved for use in children as young as 12 months old. [13,14]

Table 12. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Adults with Asthma[4]

Drug	Low dose	Medium dose	High dose
Qvar MDI (Beclomethasone) 42 mcg/puff 84 mcg/puff	168 to 504 mcg 4 to 12 puffs 2 to 6 puffs	504 to 840 mcg 12 to 20 puffs 6 to 10 puffs	>840 mcg >20 puffs >10 puffs
Pulmicort Turbuhaler (Budesonide) 200 mcg/puff	200 to 600 mcg 1 – 2 inhalations	600 to 1200 mcg 2-3 inhalations	>1200 mcg > 3 inhalations
Aerobid MDI (Flunisolide) 250 mcg/puff	500 to 1000 mcg 2 – 4 puffs	1000 to 2000 mcg 4 – 8 puffs	> 2000 mcg > 8 puffs
Flovent MDI (Fluticasone) 44, 110, 220 mcg/puff DPI (Rotadisk) 50, 100, 250 mcg/puff	88 to 264 mcg 2 to 6 puffs (44 mcg) or 2 puffs (110 mcg) 100-300 mcg 2 - 6 inhalations (50 mcg)	264 to 660 mcg 2 to 6 puffs (110 mcg) 300-600 mcg 3 – 6 inhalations (100 mcg)	>660 mcg > 6 puffs (110 mcg) or > 3 puffs (220 mcg) >600 mcg > 6 inhalations (100 mcg) or > 2 inhalations (250 mcg)
Azmacort MDI (Triamcinolone) 100 mcg/puff	400 to 1000 mcg 4 – 10 puffs	1000 – 2000 mcg 10 – 20 puffs	> 2000 mcg > 20 puffs

MDI – metered dose aerosol inhaler; Turbuhaler is a breath activated device; DPI –Dry powder inhaler

Table 13. Estimated Comparative Daily Dosages for Inhaled Corticosteroids in Children with Asthma[4]

Drug	Low dose	Medium dose	High dose
Qvar MDI (Beclomethasone) (6 – 12 years old) 42 mcg/puff 84 mcg/puff	84 to 336 mcg 2 – 8 puffs 1 – 4 puffs	336 to 672 mcg 8 – 16 puffs 4 – 8 puffs	> 672 mcg >16 puffs > 8 puffs
Pulmicort Turbuhaler (Budesonide) ≥ 6 years old 200 mcg/puff Pulmicort Respules (Budesonide inhalation suspension) (12 months to 8 years old) 0.25 mg/2 mL and 0.5 mg/2 mL	100 to 200 mcg 0.5 mg	200 to 400 mcg 1-2 inhalations 1.0 mg	> 400 mcg > 2 inhalations 1.0 mg
Aerobid MDI (Flunisolide) (6 – 15 years old) 250 mcg/puff	500 to 750 mcg 2 – 3 puffs	1000 to 1250 mcg 4 - 5 puffs	>1250 mcg > 5 puffs
Flovent (Fluticasone) MDI (≥ 12 years old) 44,110, 220 mcg/puff DPI (Rotadisk) (≥ 4 years old) 50,100, 250 mcg/dose	88 to 176 mcg 2 – 4 puffs (44 mcg) 100-200 mcg 2 – 4 inhalations (50 mcg)	176 to 440 mcg 4 –10 puffs (44 mcg) or 2 – 4 puffs (110 mcg) 200-400 mcg 2 – 4 inhalations (100 mcg)	>440 mcg > 4 puffs (110 mcg) > 400 mcg > 4 inhalations (100 mcg) or > 2 inhalations (250 mcg)

Azmacort MDI (Triamcinolone) (6 – 12 years old) 100 mcg/puff	400 to 800 mcg 4 – 8 puffs	800 to 1200 mcg 8- 12 puffs	>1200 mcg > 12 puffs

MDI – metered dose aerosol inhaler
Turbuhaler is a breath activated device
DPI –Dry powder inhaler

Effectiveness

Asthma

As discussed above in the guidelines section, inhaled corticosteroids have become the mainstay of asthma therapy, even in very young children. This differs from the 1997 report, where nedocromil and cromolyn were recommended for infants and children under 5 years of age, when chronic anti-inflammatory pharmacotherapy was indicated. Cumulative efficacy data are poor for these agents, and the potential toxicity of the inhaled corticosteroids do not negate the benefits of this therapy. [1,18,19]

Comparing the inhaled corticosteroids to each other has always been challenging because they all have differing potencies, differing bioavailabilities, and non-identical delivery devices. In general it can be said that all agents have been compared to each other, assessing changes in spirometry, peak flow rates, symptom scores, quick relief $beta_2$-agonist use, frequency of exacerbations, and airway responsiveness for different asthma severities. The overall clinical efficacy of the five marketed chemical entities appears equivalent[20-31] and the asthma guidelines do not recommend any agent over any other. Clinical efficacy differences have emerged, perhaps unfairly, when different devices are compared; the amounts of drug delivered in these circumstances are not equivalent. [32,33] More importantly, there does appear to be a difference in potential toxicity; the most potent agent fluticasone appears to have increased absorption and thus greater safety risks (see Adverse Effects section).

Combination Therapy

An important change in the treatment of asthma, reflected in the 2002 update of the asthma guidelines, is the addition of long-acting inhaled $beta_2$-agonists to inhaled corticosteroid pharmacotherapy. Outcomes can be improved, and certainly the potential adverse effect risk lowered, when a long-acting inhaled $beta_2$-agonist is added instead of raising the dose of inhaled corticosteroid.[34] This recommendation is for those with asthma greater than 5 years old. Data supporting the steroid sparing effect of other agents

(theophylline, leukotriene modifiers) is not as strong; thus these agents are considered alternative therapies.[4]

Conclusions

While inhaled corticosteroids are well accepted as asthma pharmacotherapy and are recommended as preferred therapy for all stages of persistent disease, no inhaled corticosteroid is recommended over another.

All brand products within the class reviewed are comparable to each other and none offer a significant clinical advantage over other alternatives in general use.

Recommendations

No brand inhaled corticosteroid is recommended for preferred status.

Respiratory Smooth Muscle Relaxants (AHFS Class 861600) Single Entity Products

I. Comparative Indications

Table 14 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 14. Respiratory smooth muscle relaxants Included in this Review

Generic Name	Example Brand Name
Aminophylline*	NA
Dyphylline*	Dylix, Lufyllin, Neothylline
Oxtriphylline	Choledyl SA
Theophylline anhydrous*	Accurbron, Aerolate 111, Aerolate SR, Quibron-T, Quibron-T/SR, Theo-24, Theocap, Theochron, Theolair, Theovent, Uniphyl

*Generically available

For many years, the proposed main mechanism of action for the respiratory smooth muscle relaxants was inhibition of phosphodiesterase, which results in an increase in cyclic adenosine monophosphate (cAMP). However, this effect is negligible at therapeutic concentrations. Other effects appear to occur at therapeutic concentrations and may collectively play a role in the mechanism of the xanthines. These include inhibition of extracellular adenosine (which causes bronchoconstriction), stimulation of endogenous catecholamines, antagonism of prostaglandins PGE_2 and $PGF_2\alpha$ direct effect on mobilization of intracellular calcium resulting in smooth muscle relaxation, and beta-adrenergic agonist activity on the airways. While these are potential mechanisms, none of them have been proven.[35]

Stafford, et al, tracked 1978-2002 trends in the frequency of asthma visits and patterns of asthma pharmacotherapy, focusing on the use of controller and reliever medications. Respiratory smooth muscle relaxants, which once dominated asthma therapy (63% of visits in 1978), were used in only 2% of visits in 2002. Asthma pharmacotherapy has changed extensively in the past 25 years and practices over the last decade are increasingly consistent with evidence-based guidelines.[4]

The xanthine derivatives (i.e., theophylline, dyphylline, oxtriphylline and aminophylline) that are bronchodilators are indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases (e.g., emphysema and chronic bronchitis).

II. Pharmacokinetics[35]

Table 15 includes pharmacokinetic parameters for different smooth muscle relaxant dosage formulations.

Table 15. Smooth Muscle Relaxant Formulation Pharmacokinetic Parameter Comparison

Parameter	Immediate release	Delayed-release	Extended-release
Absorption	Rapid and complete	Possibly incomplete	Varies among

			different formulations. Food and antacids may significantly alter the extent of absorption
Tmax	1-2 hours	2-4 hours	4-13 hours
Volume of Distribution	0.45L/kg		
Protein Binding	40%		
Metabolism	85%-90% hepatically metabolized		
Excretion	< 15% of drug renally excreted unchanged		

III. Drug Interactions[8]

Table 16 includes category 1 through category 5 theophylline drug interactions.

Table 16. Theophylline Drug Interactions

Category 1	Category 2	Category 3	Category 4	Category 5
Halothane	Activated Charcoal	Benzodiazepines	Allopurinol	Albuterol
	Acyclovir		Aminoglutethamide	Bitolterol
	Adenosine		Amiodarone	Caffeine
	Barbiturate		Carbamazepine	Ephedrine
	Beta Blockers (nonselective)		Corticosteroids	Famotidine
	Cimetidine		Felodipine	Furosemide
	Ciprofloxacin		Fluvoxamine	Isoetharine
	Contraceptives, Oral		Influenza Virus Vaccine	Isoproterenol
	Diltiazem		Interferon	Lansoprazole
	Disulfiram		Iodine	Loop Diuretics
	Enoxacin		Isoniazid	Metaproterenol
	Food		Ketamine	Nifedipine
	Gallamine Triethiodide		Ketoconazole	Pirbuterol
	Hydantoins		Lithium	Propofol
	Thyroid		Moricizine	Ranitidine
	Macrolide Antibiotics		Omeprazole	Sulfinpyrazone
	Methimazole		Propafenone	Terbutaline
	Metocurine Iodide		St. John's Wort	
	Mexiletine		Tacrine	
	Nondepolarizing Muscle Relaxants		Terbinafine	
	Norfloxacin		Tetracyclines	
	Primidone		Verapamil	
	Propylthiouracil		Zafirlukast	
	Rifampin			
	Thiabendazole			

	Thiamines			
	Ticlopidine			
	Zileuton			

Table 17 includes drugs interactions and how they affect theophylline levels.

Table 17. Changes in Theophylline Levels

Drugs that Decrease Theophylline Levels	Drugs that Increase Theophylline Levels
Aminoglutethimide	Allopurinol
Barbiturates	Beta blockers (non selective)
Charcoal	Calcium Channel Blockers
Hydantoins[2]	Cimetidine
Ketaconazole	Contraceptives (Oral)
Rifampin	Corticosteroids
Smoking (Cigarettes & Marijuana)	Disulfiram
Sulfinpyrazone	Ephedrine
Sympathomimetics	Influenza virus vaccine
Thioamines[3]	Interferon
Carbamazepine[1]	Macrolides
Isoniazid[1]	Mexilitene
Loop Diuretics[1]	Quinolones
	Thiabendazole
	Thyroid hormones[4]
	Carbamazepine[1]
	Isoniazid[1]
	Loop Diuretics[1]

[1] may increase or decrease theophylline levels
[2] decreased hydantoin levels may also occur
[3] increase theophylline clearance in hyperthyroid patients
[4] decreased theophylline clearance in hypothyroid patients

Drug-Food Interactions: Excessive caffeine intake may inhibit the metabolism of theophylline.[7] High-fat meals may increase and high-carbohydrate meals may decrease theophylline absorption. Food has minor effects on the absorption of Theo-Dur, Theo-Bid, Somophylline CRT, Slo-Bid, and Slophyllin; food increases the absorption of Theo-24, Theograd, Uniphyllin, and Uniphyl; food decreases the absorption of Theolair-SR and Theo-Dur Sprinkles.[36,37]

IV. Adverse Drug Events[35]

Adverse reactions/toxicity are uncommon at serum theophylline levels< 20 mcg/mL.

Levels > 20 mcg/mL:
75% of patients experience adverse reactions (e.g., nausea, vomiting, diarrhea, headache, insomnia, irritability).

Levels > 35 mcg/mL:
Hyperglycemia; hypotension; cardiac arrhythmias; tachycardia (> 10 mcg/mL in premature newborns); seizures; brain damage; death.

Cardiovascular: Palpitations; tachycardia; extrasystole; hypotension; circulatory failure; life-threatening ventricular arrhythmias.

CNS: Irritability; restlessness; headache; insomnia; reflex hyperexcitability; muscle twitching; convulsions.

GI: Nausea; vomiting; epigastric pain; hematemesis; diarrhea; rectal irritation or bleeding (aminophylline suppositories). Therapeutic doses of theophylline may induce gastroesophageal reflux during sleep or while recumbent, increasing the potential for aspiration which can aggravate bronchospasm.

Renal: Proteinuria; potentiation of diuresis.

Respiratory: Tachypnea; respiratory arrest.

Miscellaneous: Fever; flushing; hyperglycemia; inappropriate antidiuretic hormone syndrome; rash; alopecia. Ethylenediamine in aminophylline can cause sensitivity reactions, including exfoliative dermatitis and urticaria.

V. Dosing and Administration[35]

Equivalent dose:
Because of differing theophylline content, the various salts and derivatives are not equivalent on a weight basis. Table 18 indicates percentage of anhydrous theophylline and approximate equivalent dose of each compound. Product listings include anhydrous theophylline dosage equivalents.

Table 18. Theophylline Equivalent Dosing

Theophylline Content and Equivalent Dose of Various Theophylline Salts		
Theophylline salts	Theophylline %	Equivalent dose
Theophylline anhydrous	100	100 mg
Theophylline monohydrate	91	110 mg
Aminophylline anhydrous	86	116 mg
Aminophylline dihydrate	79	127 mg
Oxtriphylline	64	156 mg

Calculate dosages on the basis of lean body weight, since theophylline does not distribute into fatty tissue. Regardless of salt used, dosages should be equivalent based on anhydrous theophylline content.

Table 19 includes dosing in general use.

Table 19. Smooth Muscle Relaxant Dosing

Age	Theophylline*	Oxtriphylline	Dyphylline
1-9 years	24 mg/kg/day	6.2 mg/kg q6hrs	NA^
9-12 years	20 mg/kg/day	4.7 mg/kg q6hrs	NA^

12-16 years	18 mg/kg/day	4.7 mg/kg q6hrs	NA^
> 16 years	13 mg/kg/day	4.7 mg/kg q8hrs	Up to 15mg/kg q6hrs

*For those theophylline salts not listed, dosages should be based on equivalent anhydrous theophylline content
^Safety and efficacy has not been established in children

Individualize frequency of dosing:

- Immediate-release products - administered every 6 hours, especially in children; intervals up to 8 hours may be satisfactory in adults. Some children and adults requiring higher than average doses (those having rapid rates of clearance; e.g., half-lives < 6 hours) may be more effectively controlled during chronic therapy with sustained-release products.
- Time-release products – administered 1to 3 doses divided by 8 to 24 hours

Chronic therapy:

Slow clinical titration is generally preferred. Since these products are not necessarily interchangeable, theophylline levels should be monitored when switching from one brand to another.

Increasing dose:

The above dosage may be increased in 25% increments at 3-day intervals so long as the drug is tolerated or until the maximum dose (indicated below)is reached.

Maximum dose (where the serum concentration is not measured):
Table 20 includes maximum theophylline doses. Do not attempt to maintain any dose that is not tolerated.

Table 20. Maximum Theophylline Doses

Maximum Daily Theophylline Dose Based on Age	
Age	Maximum daily dose[1]
1 to 9 years	24 mg/kg/day
9 to 12 years	20 mg/kg/day
12 to 16 years	18 mg/kg/day
> 16 years	13 mg/kg/day

[1]Not to exceed listed dose or 900 mg, whichever is less.

VI. Effectiveness

Asthma and COPD Guidelines

Both the Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (EPR-2)[1] and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend smooth muscle relaxants as possible alternative treatment to first-line therapies.[5]

Clinical Trials

Several well-controlled studies have demonstrated the efficacy of theophylline in suppressing the symptoms of chronic asthma[38-41] and exercise-induced bronchospasm [42,43]. In one study theophylline in individualized doses resulting in an average serum concentration of 13 mcg/mL was significantly more effective in suppressing symptoms and reducing the need for emergency medication than conventional doses combined with ephedrine at an average serum concentration of 6.5 mcg/mL or placebo[38]. Furthermore, even in patients with steroid-dependent asthma, the addition of therapeutic doses of theophylline decreased symptoms, improved exercise tolerance, and decreased the need for inhaled sympathomimetics and short courses of daily corticosteroids during exacerbations as compared to placebo when both were added to the chronic steroid regimen[40].

VII. Conclusions

Since guidelines recommend smooth muscle relaxants as possible alternatives to first-line therapies for asthma and COPD, these agents can be compared on indications, pharmacokinetics, drug interactions, adverse drug events, and dosing and administration. All brand products within the smooth muscle relaxant class are comparable to each other and to generics in this class and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand single entity smooth muscle relaxant is recommended for preferred status.

Respiratory Smooth Muscle Relaxants (AHFS Class 861600) Combination Products

I. Comparative Indications[35]

To compliment smooth muscle relaxants bronchodilator properties, agents such as guaifenesin or sympathomimetics are combined in a single dosage formulation. Guaifenesin is included in products to mobilize mucus. Sympathomimetics may be included for bronchodilation or decongestant properties, although pseudoephedrine is not an effective bronchodilator. While the individual agents have different pharmacologic effects, these products present two problems: (1) The patient may not need the components of the product; (2) the patient may need the components, but in different strengths or intervals. Additionally, titrating theophylline doses to achieve a therapeutic serum drug level is now compounded by the addition of another pharmaceutical product that has a maximum daily amount.

Table 21 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 21. Smooth Muscle Relaxant Products in this Review

Brand Name Example(s)	Xanthine	Expectorant	Sympathomimetic
Quibron, Theolate, Elixophyllin GG, Broncomar GG, ED-Bron G, Quelan, Quibron, Thoemar	Theophylline	Guaifenesin	
COPD, Difil-G, Difil-G Forte, Dilor-G, Dylex-G, Dyfilin GG, Dyflex, Dyline GG, Dyphyl-G, Lufyllin-GG, Panfil G, Dilor-G,	Dyphylline	Guaifenesin	
Brondelate	Oxtriphylline	Guaifenesin	
Elixophyllin-KI	Theophylline	Potassium Iodide	
Broncomar-1	Theophylline	Guaifenesin	Pseudoephedrine
Broncomar	Dyphylline	Guaifenesin	Pseudoephedrine

The xanthine derivatives (i.e., theophylline, dyphylline, oxtriphylline and aminophylline) are bronchodilators indicated for the treatment of the symptoms and reversible airflow obstruction associated with chronic asthma and other chronic lung diseases (e.g., emphysema and chronic bronchitis).

II. Pharmacokinetics[35]

Table 22 includes pharmacokinetic parameters for expectorant and sympathomimetic products included in these formulations. Smooth muscle relaxant pharmacokinetics have been previously reviewed (see page 19).

Table 22. Smooth Muscle Relaxant Formulation Pharmacokinetic Parameter Comparison

Parameter	Guaifenesin	Potassium Iodide	Pseudoephedrine
Absorption	Readily absorbed	Absorbed as iodinated	-

		amino acids	
Tmax	-	-	½ - 1 hour
Distribution	-	Largely extracellularly	Widely distributed
Metabolism	60% hepatically metabolized	-	Partially metabolized in liver
Excretion	Renally eliminated as β-(2-methoxyphenoxy) lactic acid and unchanged drug	Renally eliminated	70%-90% renally excreted as unchanged drug
Half life	1 hour	-	9-16 hours

III. Drug Interactions[8,44]

Theophylline drug interactions have previously been reported. There are no clinically significant drug interactions associated with guaifenesin use. Below are the clinically significant drug interactions for the other agents.

Potassium Iodide

- **Category 1 – amiloride, potassium-sparring diuretics (e.g., spironolactone and triamterene)**
- **Category 2 - lithium**

Pseudoephedrine

- **Category 1 – furazolidone, MAO inhibitors**
- **Category 2 – guanethidine, methyldopa, potassium citrate, sodium acetate, sodium bicarbonate, sodium citrate, sodium lactate, tromethamine, urinary alkalinizers**

IV. Adverse Drug Events[35]

Guaifenesin

Nausea, vomiting, GI discomfort (most common); dizziness, headache, rash (including urticaria) (rarely reported).

Potassium Iodide

Thyroid adenoma; goiter; myxedema. Hypersensitivity may be manifested by angioneurotic edema, cutaneous and mucosal hemorrhages and symptoms resembling serum sickness, such as fever, arthralgia, lymph node enlargement and eosinophilia.

Miscellaneous**:**

GI bleeding; confusion; irregular heartbeat; numbness; tingling; pain or weakness in hands or feet; unusual tiredness; weakness or heaviness of legs; fever; swelling of neck or throat; thyroid gland enlargement, acute parotitis (rare).

Chronic iodine poisoning***:***

This or iodism may occur during prolonged treatment. Symptoms include: metallic taste; burning of mouth or throat; soreness of the mouth, teeth and gums; ulceration of mucous

membranes; increased salivation; coryza; sneezing; swelling of the eyelids. Gastric disturbance, nausea, vomiting, epigastric pain and diarrhea are common. There may be a severe headache, productive cough, pulmonary edema and swelling and tenderness of the salivary glands. Acneiform skin lesions are seen in the seborrheic areas. Severe and sometimes fatal skin eruptions may develop. If iodism appears, withdraw the drug and institute appropriate supportive therapy.

Pseudoephedrine:
Palpitations, tachycardia, PVCs, arrhythmias, skipped beats, dizziness/vertigo, shakiness/nervousness/tension, headache, insomnia, nausea/vomiting, sweating and anorexia/appetite loss.

V. Dosing and Administration[35]

Dosing of smooth muscle relaxant combination products needs to be based on the theophylline agent taking care not to exceed maximum doses of the other ingredients in the combination product (refer to pages 22-23).

VI. Effectiveness

Asthma and COPD Guidelines [1,4,5]

Neither the Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (EPR-2)[1] nor the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines directly address the smooth muscle relaxant combination products.

VII. Conclusions

Since guidelines do not address the use of these medications and there are no clinical head-to-head trials, these agents can be compared on indications, pharmacokinetics, drug interactions, adverse drug events, and dosing and administration. All brand products within the smooth muscle relaxant combination product class are comparable to each other and to generics in this class and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand smooth muscle relaxant combination product is recommended for preferred status.

Single Entity Sympathomimetic Agents (AHFS Class 121200)

I. Comparative Indications

The sympathomimetics are used to relieve bronchospasm associated with bronchial asthma, exercise-induced bronchospasm (EIB), bronchitis, emphysema, bronchiectasis or other obstructive pulmonary diseases. Sympathomimetics relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles and therefore producing bronchodilation.

Table 23 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 23. Sympathomimetics Products in this Review

Generic Name	Brand Name Examples
Albuterol	AccuNeb, Airet, Proventil, Ventolin, Volmax,
Ephedrine	NA
Epinephrine	NA
Formoterol	Foradil
Isoetharine	NA
Isoproterenol	Isuprel
Levalbuterol*	Xopenex
Metaproterenol	Alupent
Pirbuterol	Maxair
Salmeterol	Serevent
Terbutaline	Brethine

*Not generically available

The pharmacologic actions of the sympathomimetic agents include: alpha-adrenergic stimulation (vasoconstriction, nasal decongestion, pressor effects); β_1-adrenergic stimulation (increased myocardial contractility and conduction); and β_2-adrenergic stimulation (bronchial dilation and vasodilation, enhancement of mucociliary clearance, inhibition of cholinergic neurotransmission). Beta-adrenergic drugs stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Cyclic AMP that is formed inhibits the release of mediators of immediate hypersensitivity from inflammatory cells, especially from mast cells and basophils. This increase of cyclic AMP leads to activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation.[2]

Other adrenergic actions include alpha receptor-mediated contraction of GI and urinary sphincters; α and β receptor-mediated lipolysis; α and β receptor-mediated decrease in GI tone; and changes in renin secretion, uterine relaxation, hepatic glycogenolysis/gluconeogenesis, and pancreatic beta cell secretion.[2]

The relative selectivity of action of sympathomimetic agents is the primary determinant of clinical usefulness; it can predict the most likely side effects. Beta$_2$-selective agents

provide the greatest benefit with minimal side effects. Direct administration via inhalation provides prompt effects and minimizes systemic activity. These drugs also inhibit histamine release from mast cells, produce vasodilation, and increase ciliary motility. Isoproterenol is one of the most potent bronchodilators available. [2]

Table 24 lists approved FDA indications for the sympathomimetics.

Table 24. Sympathomimetic Indications [6,45-59]

Generic Name	Brand Name Example(s)	Indications
Albuterol	Ventolin, Proventil	For relief and prevention of bronchospasm in patients with reversible obstructive airway disease; acute attacks of bronchospasm (inhalation solution); prevention of exercise-induced bronchospasm. Tablets are indicated for children ≥ 6 years of age; aerosol and inhalation powder are indicated for children ≥ 4 years of age (≥ 12 years of age for Proventil); syrup and solution for inhalation are indicated for children ≥ 2 years of age.
Ephedrine	Various	**Ephedrine sulfate injection is indicated in the treatment of allergic disorders, such as bronchial asthma and for the relief of acute bronchospasm. Oral ephedrine is indicated for temporary relief of shortness of breath, tightness of chest, wheezing, and for easing breathing in bronchial asthma.**
Epinephrine	Various	For temporary relief of shortness of breath, tightness of chest, and wheezing of bronchial asthma; post intubation and infectious croup. ***microNefrin:*** Chronic obstructive lung disease, chronic bronchitis, bronchiolitis, bronchial asthma, and other peripheral airway diseases; croup (post intubation and infectious).
Formoterol	Foradil	Asthma/Bronchospasm: For long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in adults and children ≥ 5 years of age with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting, $beta_2$-agonists. It is not indicated for patients whose asthma can be managed by occasional use of inhaled, short-acting, $beta_2$-agonists. Prevention of exercise-induced bronchospasm (EIB): For the acute prevention of EIB in adults and children ≥12 years of age when administered on an occasional, as-needed basis. Concomitant therapy: Can be used concomitantly with short-acting $beta_2$-agonists, inhaled or systemic corticosteroids, and theophylline therapy. A satisfactory clinical response to formoterol does not eliminate the need for continued treatment with an anti-inflammatory.

Generic Name	Brand Name Example(s)	Indications
		Chronic obstructive pulmonary disease (COPD): For long-term, twice daily (morning and evening) administration in the maintenance of bronchoconstriction in patients with COPD including chronic bronchitis and emphysema.
Isoetharine		For bronchial asthma and reversible bronchospasm that occurs with bronchitis and emphysema.
Isoproterenol	Isuprel	For bronchospasm during anesthesia.
Levalbuterol	Xopenex	For the treatment or prevention of bronchospasm in adults, adolescents, and children 6 years of age and older with reversible obstructive airway disease.
Metaproterenol	Alupent	For bronchial asthma and reversible bronchospasm that may occur in association with bronchitis and emphysema; treatment of acute asthmatic attacks in children $\geq$ 6 years of age (5% solution for inhalation *only*).
Pirbuterol	Maxair	For prevention and reversal of bronchospasm in patients with reversible bronchospasm including asthma. Use with or without concurrent theophylline or corticosteroid therapy.
Salmeterol	Serevent	Asthma/Bronchospasm: For long-term, twice-daily (morning and evening) administration in the maintenance treatment of asthma and in the prevention of bronchospasm in patients 12 years of age and older (4 years of age and older for inhalation powder) with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma who require regular treatment with inhaled, short-acting β_2-agonists. Do not use in patients whose asthma can be managed by occasional use of short acting, inhaled β_2-agonists. Salmeterol may be used alone or in combination with inhaled or systemic corticosteroid therapy. Exercise-induced bronchospasm (EIB): Prevention of EIB in patients 12 years of age and older (4 years of age and older for inhalation powder). Chronic obstructive pulmonary disease (COPD): Long-term, twice-daily (morning and evening) administration in the maintenance treatment of bronchospasm associated with COPD (including emphysema and chronic bronchitis).
Terbutaline	Brethine	For prevention and reversal of bronchospasm in patients $\geq$ 12 years of age with asthma and reversible bronchospasm associated with bronchitis and emphysema.

II. Pharmacokinetics[6,45-59]

Table 25 includes pharmacokinetic parameters for the sympathomimetic products included in these review.

Table 25. Sympathomimetic Pharmacokinetic/Pharmacologic Properties

Sympathomimetic	Adrenergic receptor activity	β_2 potency[1]	Route	Onset (minutes)	Duration (hrs)
Albuterol	$\beta_1 < \beta_2$	2	PO	within 30	4-8
			Inhaled	within 5	3-6
Ephedrine	α, β_1, β_2	--	PO	15-60	3-5
			SC	> 20	$\geq$ 1
			IM	10-20	$\geq$ 1
			IV	immediate	--
Epinephrine	α, β_1, β_2	--	SC	5-10	4-6
			IM	--	1-4
			Inhaled	1-5	1-3
Formoterol	$\beta 2$	--	Inhaled	10	12
Isoetharine	$\beta_1 < \beta_2$	6	Inhaled	within 5	2-3
Isoproterenol	β_1, β_2	1	IV	immediate	< 1
			Inhaled	2-5	1-3
Levalbuterol	β_2	--	Inhaled	10	5-6
Metaproterenol	$\beta_1 < \beta_2$	15	PO	±30	4
			Inhaled	5-30	1- $\geq$ 6
Pirbuterol	$\beta_1 < \beta_2$	5	Inhaled	within 5	5
Salmeterol	$\beta_1 < \beta_2$	0.5	Inhaled	Within 20	12
Terbutaline	$\beta_1 < \beta_2$	4	PO	30	4-8
			SC	5-15	1.5-4
			Inhaled	5-30	3-6

[1]Relative molar potency:1 = most potent.

III. Drug Interactions[6,45-59]

Most interactions listed in Table 26 apply to sympathomimetics when used as vasopressors; however, consider these interaction when using the sympathomimetics as bronchodilators.

Table 26. Sympathomimetic Bronchodilator Drug Interactions

Precipitant drug	Object drug*		Description
Beta blockers	Sympathomimetics	↓	Concomitant use may inhibit cardiac, bronchodilating, and vasodilating effects. Severe bronchospasms may be produced in asthmatic patients taking albuterol or salmeterol. Consider cardioselective beta blockers, and use with caution if there are no alternatives to beta blocker therapy. With epinephrine, an initial hypertensive episode followed by bradycardia may occur.
Furazolidone	Sympathomimetics	↑	The pressor sensitivity to mixed-acting sympathomimetics(eg, ephedrine) may be increased. Direct-acting agents (eg, epinephrine) are not affected.
Guanethidine	Sympathomimetics		Guanethidine potentiates the effects of the direct-acting sympathomimetics (e.g., epinephrine) and inhibits the effects of the mixed-acting agents (e.g., ephedrine). Guanethidine hypotensive action may also be reversed, requiring increased guanethidine dosage.
	Direct	↑	
	Mixed	↓	
Sympathomimetics	Guanethidine	↓	
Methyldopa	Sympathomimetics	↑	Concurrent administration may result in an increased pressor response.
MAO inhibitors	Sympathomimetics	↑	Coadministration of MAO inhibitors and mixed-acting sympathomimetics (e.g., ephedrine) may result in severe headache, hypertension, and hyperpyrexia, resulting in hypertensive crisis. MAO inhibitors also potentiate the actions of beta-adrenergic agonists on the vascular system. Direct-acting agents (e.g., epinephrine) interact minimally. Avoid coadministration with sympathomimetics or within 2 weeks.
Oxytocic drugs (eg, ergonovine)	Sympathomimetics	↓	Concurrent administration may result in severe hypotension.
Rauwolfia alkaloids	Sympathomimetics		Reserpine potentiates the pressor response of the direct-acting sympathomimetics (e.g., epinephrine), which may result in hypertension. The pressor response of the mixed-acting agents (e.g., ephedrine) is decreased.
	Direct	↑	
	Mixed	↓	
Tricyclic antidepressants	Sympathomimetics		TCAs potentiate the pressor response of direct-acting sympathomimetics (e.g., epinephrine);
	Direct	↑	

Precipitant drug	Object drug*		Description
(TCAs)	Mixed	↓	dysrhythmias have occurred. The pressor response of mixed-acting agents (eg, ephedrine) is decreased. TCAs also potentiate the actions of beta-adrenergic agonists on the vascular system.
Sympathomimetics	Theophylline	↔	Enhanced toxicity, particularly cardiotoxicity, has been noted. Decreased theophylline levels may occur. Ephedrine may cause theophylline toxicity.
General anesthetics (eg, halothane, cyclopropane)	Isoproterenol Epinephrine Ephedrine	↑	The potential for the myocardium to be sensitized to the effects of sympathomimetic amines is increased. Arrhythmias may result with coadministration and may respond to beta blockers.
Cardiac glycosides			
Alpha-adrenergic blockers (eg, phentolamine)	Ephedrine Epinephrine	↓	Vasoconstricting and hypertensive effects are antagonized.
Diuretics	Ephedrine Epinephrine	↓	Vascular response may be decreased.
Antihistamines	Epinephrine	↑	Epinephrine effects may be potentiated.
Ergot alkaloids Phenothiazines Nitrites	Epinephrine	↓	Pressor effects of epinephrine may be reversed.
Levothyroxine	Epinephrine	↑	Epinephrine effects may be potentiated.
Epinephrine	Insulin or oral hypoglycemic agents	↓	Diabetics may require an increased dose of the hypoglycemic agent.
Ergot alkaloids	Isoproterenol	↑	Coadministration may result in additive peripheral vasoconstriction.
Isoproterenol	Ergot alkaloids		
Albuterol Salmeterol	Diuretics	↑	ECG changes and hypokalemia associated with these diuretics may worsen with coadministration.
Albuterol	Digoxin	↓	Digoxin serum levels may be decreased.

IV. Adverse Drug Events[6,45-59]

Table 27 lists possible adverse drug events associated with sympathomimetic use.

Table 27. Sympathomimetic Adverse Drug Events (%)

Adverse reaction		Albuterol[1]	Levalbuterol[2]	Isoetharine[1]	Metaproterenol[1]	Pirbuterol[1]	Terbutaline[1]	Isoproterenol[1]	Ephedrine[1]	Epinephrine[1]	Salmeterol[1]	Formoterol[2]
Cardiovascular	Palpitations	< 1-10		√	0.3-4	1.3-1.7	≤23	< 5-22	√	7.8-30	1-3	
	Tachycardia	1-10	2.7	√	< 17	1.2-1.3	1.3-3	2-12	√	≤2.6	1-3	
	Blood pressure changes/hypertension	1-5		√	0.3		< 1	2-5		√		
	Chest tightness/pain/discomfort, angina	< 3			0.2	< 1.3	1.3-1.5	√		≤2.6		
	PVCs, arrhythmias, skipped beats					< 1	±4	< 1-3	√	√		
CNS	Tremor	< 1-24.2	6.8	√	1-33	1.3-6	< 5-38	< 15		16-18	4	1.9
	Dizziness/vertigo	< 1-7	2.7	√	1-4	0.6-1.2	1.3-10	1.5-5	√	3.3-7.8	≥ 3	1.6
	Shakiness/nervousness/tension	1-20	9.6	√	2.6-14	4.5-7	< 5-31	< 15	√	8.5-31	1-3	
	Weakness	< 2		√	1.3	< 1	≤1.3	√		1.6-2.6		
	Drowsiness	< 1			0.7		< 5-11.7	< 5		8.2-14		
	Restlessness	< 1		√						√		
	Hyperactivity/Hyperkinesia, excitement	1-20		√		< 1		√				
	Headache	2-22		√	≤4	1.3-2	7.8-10	1.5-10	√	3.3-10	28	
	Insomnia	1-11		√	1.8	< 1	√	1.5	√	√		1.5
GI	Nausea/Vomiting	2-15		√	< 14	≤1.7	1.3-10	< 15	√	1-11.5	1-3	
	Heartburn/GI distress/ disorder	≤5			≤4		< 10	≤5-10			1-3	
	Diarrhea	1			0.7	< 1.3						
	Dry mouth	< 3			1.3	< 1.3						
Respiratory	Cough	< 1-5	4.1		≤4	1.2		1-5			7	
	Wheezing	≤1.5					√	1.5				
	Dyspnea	1.5					≤2	≤1.5		≤2		2.1
	Bronchospasm	1-15.4						≤18				
	Throat dry-ness/irritation, pharyngitis	≤6			≤4	< 1	√	3.1			≥ 3	
Miscellaneous	Flushing	< 1				< 1	≤2.4	√		≤1.3		
	Sweating	< 1					≤2.4	√	√	√		
	Anorexia/Appetite loss	1				< 1			√	√		
	Unusual/bad taste or taste/smell change	< 1			≤0.3	< 1	√					

[1]Data pooled for all routes of administration, all age groups, from separate studies, and are not necessarily comparable.

[2]Obtained from each product's respective package labeling. √=Reported but no incidence given.

In January 2003, GlaxoSmithKline notified providers of the Salmeterol Multi-center Asthma Research Trial (SMART) safety trial results and of package labeling changes. A warning statement was included to notify providers of a small but significant increase in asthma-related deaths in patients receiving salmeterol (i.e., 13 deaths out of 13,174 patients treated with salmeterol) versus placebo (i.e., 4 or 13,179). This risk may be greater in African-American patients.

V. Dosing and Administration[6,45-59]

Medication	***Dosing and Administration***
Albuterol	**Inhalation aerosol:** • Acute therapy: 2 inhalations every 4 to 6 hours. • Maintenance therapy (Proventil only): 2 inhalations 4 times/day • Prevention of exercise-induced bronchospasm: 2 inhalations 15 minutes prior to exercise **Inhalation solution:** • Adults and children ≥ 12 years of age: 2.5 mg 3 to 4 times/day by nebulization. • Children 2 to 12 years of age (≥ 15 kg): 2.5 mg (1 UD vial) 3 to 4 times/day by nebulization. • AccuNeb: The usual starting dosage for patients 2 to 12 years of age is 1.25 mg or 0.63 mg administered 3 or 4 times/day, as needed, by nebulization. **Tablets:** • Adults and children ≥ 12 years of age: 2 or 4 mg 3 or 4 times/day. Do not exceed a total daily dose of 32 mg. • Children 6 to 12 years of age: 2 mg 3 to 4 times/day. Do not exceed a total daily dose of 24 mg (given in divided doses). • Elderly and those sensitive to ß-adrenergic stimulants: Start with 2 mg 3 or 4 times/day. If adequate bronchodilation is not obtained, increase dosage gradually to as much as 8 mg 3 or 4 times/day. **Tablets, extended-release:** • 4-8mg every 12 hours • Switching to extended-release tablets: • Patients maintained on regular-release albuterol can be switched to Proventil Repetabs or Volmax extended-release tablets. A 4 mg extended-release tablet every 12 hours is equivalent to a regular 2 mg tablet every 6 hours. **Syrup:** • Adults and children > 12 years of age: 2 or 4 mg (1 to 2 teaspoonfuls;5 to 10 mL) 3 or 4 times/day. • Children (6 to 12 years of age): 2 mg (1 teaspoonful; 5 mL)3 or 4 times/day. • Children (2 to 6 years of age): Initiate at 0.1 mg/kg 3 times/day. The starting dose should not exceed 2 mg 3 times/day. • Elderly and those sensitive to ß-adrenergic stimulation: Restrict initial dose to 2 mg (1 teaspoonful; 5 mL) 3 or 4 times/day.
Ephedrine	**Oral:** • Adults and children ≥ 12 years of age: 12.5 to 25 mg every 4 hours, not to exceed 150 mg in 24 hours. • Children < 12 years of age: For use in children < 12 years of age, consult a physician. **Parenteral:** • Adults: 25 to 50 mg (range, 10 to 50 mg) administered SC or IM, or 5 to 25 mg administered slowly IV repeated every 5 to 10 minutes, if necessary. • Children: The usual SC, IV, or IM dose is 0.5 to 0.75 mg/kg or 16.7 to 25 mg/m^2 every 4 to 6 hours.
Epinephrine	**Inhalation aerosol:** • Adults and children ≥ 4 years of age: Start with 1 inhalation, then wait ≥ 1 minute. If not relieved, use once more. Do not use again for ≥ 3 hours.

	Nebulization: • Adults and children ≥ 4 years of age: Add 0.5 mL (10 drops) racemic epinephrine into nebulizer reservoir; add 3 mL of diluent or 0.2 to 0.4 mL (to 8 drops) of microNefrin to 4.6 to 4.8 mL water. Administer for 15 minutes every 3 to 4 hours.

Isoetharine

Isoetharine Doses

Method of administration	Usual dose	Range of dose of 1:3 dilution[1]
Hand bulb nebulizer	4 inhalations	3 to 7 inhalations undiluted
Oxygen aerosolization[2]	0.5 mL	1 to 2 mL
IPPB[3]	0.5 mL	1 to 4 mL

[1]Dilution of 1 part isoetharine plus 3 parts of normal saline solution.
[2]Administered with oxygen flow adjusted to 4 to 6 L/min over 15 to 20 minutes.
[3]IPPB = intermittent positive pressure breathing. Usually an inspiratory flow rate of 15 L/min at a cycling pressure of 15 cm H_2O is recommended. It may be necessary, according to patient and type of IPPB apparatus, to adjust flow rate to 6 to 30 L/min, cycling pressure to 10 to 15 cm H_2O, and further dilution according to the needs of the patient.

Levalbuterol

Children 6 to 11 years of age:
The recommended dosage is 0.31 mg administered 3 times/day by nebulization. Do not exceed routine dosing of 0.63 mg 3 times/day.

Adults and adolescents 12 years of age or older:
The recommended starting dosage is 0.63 mg administered 3 times/day(every 6 to 8 hours) by nebulization.

Metaproterenol

Aerosol:
2 to 3 inhalations every 3 to 4 hours. Do not exceed 12 inhalations/day. Not recommended for children < 12 years of age.

Solution for inhalation:

Dosage and Dilution for Metaproterenol Solutions for Inhalation 5%

Administration	Usual dose	Range	Dilution
Adults and children ≥ 12 years of age			
Hand bulb nebulizer	10 inhalations	5 to 15 inhalations	No dilution
IPPB or nebulizer	0.3 mL	0.2 to 0.3 mL	In ≈2.5 mL saline or other diluent
Children 6 to 12 years of age			
Nebulizer	0.1 mL	0.1 to 0.2 mL	In saline to a total volume of 3 mL

Pirbuterol

Adults and children > 12 years of age:
2 inhalations (0.4 mg) repeated every 4 to 6 hours. One inhalation (0.2 mg) may be sufficient for some patients.

Terbutaline

Oral:
- Adults > 15 years of age: 5 mg given at 6-hour intervals, 3 times/day during waking hours. If side effects are pronounced, dose may be reduced to 2.5 mg 3 times/day. Do not exceed 15 mg in 24 hours.
- Children (12 to 15 years of age):2.5 mg 3 times/day. Not recommended for children< 12 years of age. Do not exceed 7.5 mg in 24 hours.

Parenteral:
- 0.25 mg SC into the lateral deltoid area. If significant improvement does not occur in 15 to 30 minutes, administer a second 0.25 mg dose. If a patient fails to respond to a second 0.25 mg dose within 15 to 30 minutes, consider other therapeutic measures. Do not exceed a total dose of 0.5 mg in 4 hours.

Medication

Dosing and Administration [2, 20,25]

Formoterol

Asthma/Bronchospasm:
- For adults and children ≥ 5 years of age; One x 12 mcg formoterol capsule every 12 hours.

	Prevention of EIB: • For adults and adolescents ≥ 12 years of age, the usual dosage is the inhalation of the contents of one 12 mcg formoterol capsule ≥ 15 minutes before exercise, administered on an occasional as-needed basis. **Maintenance treatment of COPD:** • One x 12 mcg formoterol capsule every 12 hours
Salmeterol	**Asthma/Bronchospasm:** • Aerosol: 2 inhalations (42 mcg) twice/day (morning and evening, approximately 12 hours apart). • Inhalation powder: 1 inhalation (50 mcg) twice/day (morning and evening, approximately 12 hours apart). **Prevention of EIB:** • Aerosol: Two inhalations of the aerosol at least 30 to 60 minutes before exercise protects against EIB in many patients for up to 12 hours. • Inhalation powder: One powder inhalation at least 30 minutes before exercise protects patients against EIB. **COPD:** • Aerosol: 2 inhalations (42 mcg) twice daily (morning and evening), approximately 12 hours apart. • Inhalation powder: 1 powder inhalation(50 mcg) twice daily (morning and evening), approximately 12 hours apart.

VI. Effectiveness

Both the Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma (EPR-2)[1] and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend sympathomimetic therapy as central to symptom management but do not recommend one specific agent over another.[1,4,5]. Additionally, other studies have reported comparable sympathomimetics and respective treatment modalities to be equally effective in the treatment of asthma.[64-67] However, the COPD guidelines discuss that long-acting bronchodilators are more effective than short acting agents and that regular use improves health status. Also, long-acting sympathomimetic therapy provides additional benefits in long-term control of asthma.

Safety, however, may be an issue in this category as at least one study (SMART) has suggested a link between salmeterol and increased life threatening episodes-including deaths. These findings, although concerning, were not statistically significant so more analysis must be done to confirm the findings. The FDA has also stated "the benefits of treatment with salmeterol in patients with asthma and COPD continue to outweigh the potential risks when used according to the instructions contained in the product labeling."[59] It has not been determined whether these findings are related only to salmeterol or are a class effect.

Table 28 summarizes outcomes from studies comparing levalbuterol and albuterol in the treatment of asthma and COPD.

Table 28. Levalbuterol vs. Albuterol Clinical Studies

Study	Sample	Duration	Results
Nelson, et al.[68]	n=362 adult outpatient asthma (FEV_1 45%-70% of predicted) clinic patients with chronic stable asthma; compared placebo, levalbuterol 0.63mg, levalbuterol, 1.25mg, albuterol 1.25mg and albuterol 2.5mg.	4 weeks	• Compared to albuterol, levalbuterol had significant improvement in: o FEV_1 and FEV_1 AUC after first dose but not at week 4. o predose FEV_1 in patients not receiving inhaled corticosteroids. • All treatments well tolerated.
Carl, et al.[69]	n=482 children (1-18 years of age) seen in the emergency department and inpatient asthma care unit; compared levalbuterol 1.25mg to 2.5mg albuterol.	NA	• Hospitalization rate significantly lower in levalbuterol vs. albuterol group (36% vs. 45%, respectively). • Adjusted relative risk for admission was 1.25 for levalbuterol (95% CI, 1.01 –1.51). • No difference in ED or hospital length of stay, aerosol use or adverse effects.
Milgrom, et al.[70]	n=338 children (4-11 years of age) with asthma (FEV_1 40%-85% of predicted); compared levalbuterol (0.31mg or 0.63mg), albuterol (1.25mg or 2.5mg), or placebo	21 days	• No difference in FEV_1 change at day 21. • Significant improvement in FEV_1 immediately after nebulization better for levalbuterol 0.31mg and 0.63mg vs. albuterol 1.25mg. • Levalbuterol 0.31mg did not differ from placebo for changes in ventricular rate, QT_c interval and glucose. • No difference in asthma symptom assessment score, symptom-free days, and QOL score. • Similar rescue medication use.
Gawchik, et al.[71]	n=33 children (3-11 years of age) with asthma (FEV_1 50-80% of predicted); dose escalation using levalbuterol 0.16mg, 0.31mg, 0.63mg and 1.25mg vs albuterol 1.25mg and 2.5mg.	32 days	• All treatment arms had significant FEV_1 changes compared to placebo. • No differences in FEV_1 percent change between active treatments. • All treatments well tolerated.
Datta, et al.[72]	n=30 elderly patients with COPD (FEV_1 45-70& of predicted); double-blind crossover trial comparing single doses of albuterol 2.5mg, levalbuterol 1.25mg, albuterol 2.5mg + ipratropium, and placebo		• Similar improvements in FEV_1 at 30, 60 and 120 mins following drug administration. • Mild increase in pulse rate in all treatment arms.

VII. Conclusions

In the long-term treatment of asthma and COPD, long-acting sympathomimetics offer a clinical advantage over other sympathomimetics. Brand versions of formoterol (Foradil) and salmeterol (Serevent) offer significant clinical advantage in general use over the other brands and generics in the same class but are comparable to each other.

VIII. Recommendations

Medicaid should work with manufacturers of the recommended brands of Foradil and Serevent on cost proposals so that at least one of the recommended brands is selected as a preferred agent.

Sympathomimetic Combination Agents (AHFS Class 121200)

Comparative Indications[35,74-76]

Table 29 lists the two products included in this review. This review encompasses all dosage forms and strengths.

Table 29. Antimuscarinic/Antispasmodic Combination Products in this Review*

Oral Inhalation	Generic Name	Brand Names Example (s)
Aerosol	Albuterol Sulfate / Ipratropium Bromide	Combivent
Solution for Nebulization	Albuterol Sulfate / Ipratropium Bromide	DuoNeb
Powder	Fluticasone/Salmeterol	Advair

*No products currently available in generic formulations

Combivent and DuoNeb are both indicated for bronchospasm in patients with COPD, on a regular aerosol bronchodilator, who continue to have evidence of bronchospasm and require a second bronchodilator.[8] Combining more than one bronchodilator with different mechanisms and durations of action may increase the degree of bronchodilation for equivalent or lesser side effects. Nebulized therapy for a stable patient is not appropriate unless it has been shown to be better than conventional doses by metered dose inhaler.

Advair is indicated for the long-term, maintenance treatment of asthma in patients 12 years of age and older. It is also indicated for maintenance treatment of airflow obstruction in patients with COPD associated with chronic bronchitis.

Pharmacokinetic Parameters[35,74-76]

Ipratropium Bromide (Table 6): Bronchodilation following administration of ipratropium results primarily in local, site-specific effects. The drug is not absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract. Following administration via inhalation, bronchodilation is evident within 15 minutes, is maximal within 1-2 hours, and may persist for up to 6 hours.[77] A large portion of the drug administered is swallowed and excreted in the feces. The drug is minimally bound (0-9%) to plasma albumin and alpha$_1$-acid glycoprotein and is partially metabolized to inactive ester hydrolysis products. The elimination half-life of ipratropium is about 2 hours.

Albuterol Sulfate: Unlike ipratropium, albuterol is rapidly and completely absorbed. Studies indicate that less than 20% of a single dose of albuterol inhalation solution, given by nebulization, is absorbed.[77] It has been shown that

less than 10% of an orally inhaled dose of albuterol reaches the bronchial tree. Bronchodilation begins within 5-15 minutes after oral inhalation via a metered-dose inhaler, lasting 2-5 hours, while bronchodilation after nebulization begins within 5 minutes, lasting 3-4 hours. The drug is conjugatively metabolized to albuterol 4-O-sulfate. Intravenous studies have shown that albuterol does cross the blood-brain barrier and reached concentrations of about 5% of the plasma concentrations. In structures outside the blood-brain barrier, the drug achieved concentrations more than 100 times those in the whole brain.

Combivent: In a crossover pharmacokinetic study comparing the pharmacokinetic parameters of Combivent Inhalation Aerosol to the two active components individually, the co-administration of albuterol and ipratropium from a single canister did not significantly alter the systemic absorption of either component. The synergistic efficacy of Combivent is likely to be due to a local effect on the muscarinic and $beta_2$-adrenergic receptors in the lung.

DuoNeb: A double blind, crossover study of albuterol alone compared to DuoNeb showed the mean peak albuterol concentration following administration of albuterol was 4.86 (± 2.65) mg/ml and it was 4.65 (±2.92) mg/ml for DuoNeb. Mean AUC values for the two treatments were 26.6 (±15.2) ng•hr/ml (albuterol alone) versus 24.2 (+14.5) ng•hr/ml (DuoNeb). The mean half-life values were 7.2 (±1.3) hours for albuterol and 6.7 (±1.7) hours for DuoNeb. There were no statistically significant differences in the pharmacokinetics of albuterol between the two treatments. For ipratropium, a mean of 3.9 (±5.1)% was excreted unchanged in the urine, which is comparable with previously reported data.

Advair: Following administration of Advair to healthy subjects, peak plasma concentrations of fluticasone were achieved in 1 to 2 hours and those of salmeterol were achieved in about 5 minutes. In two studies, patients were given inhalations of Advair Diskus and fluticasone powder alone. No significant changes in systemic exposure to fluticasone were found when administered with salmeterol or separately.

Drug Interactions[35,74-76]

There are no clinically significant drug interactions that place the combination of albuterol / ipratropium at a disadvantage compared to either individual drug alone. In fact, there are no level 1, 2, or 3 (clinically significant) interactions documented with albuterol or ipratropium individually. However, the package insert for Combivent specifically states no formal drug interaction studies have been performed with the combination inhalation aerosol product.

Although ipratropium is minimally absorbed, there is a small potential for an additive interaction with concomitantly used anticholinergic medications. Thus, caution should be used in the co-administration of the combination treatment with other anticholinergic drugs. In addition, caution should be used when the combination treatments are used with other sympathomimetic agents, due to

increased risk of adverse cardiovascular effects (with albuterol). DuoNeb and Combivent should be administered only with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within two weeks of discontinuation of such agents, due to the potential for the cardiovascular actions of albuterol to be exacerbated. Finally, use of beta-agonists, especially when the recommended dose of the beta-agonist is exceeded, with non-potassium sparing diuretics, should be avoided if possible due to acutely worsened ECG changes and / or hypokalemia. Other less significant interactions documented with albuterol include: digoxin, aminophylline, and theophylline.

Advair Discus had been used concomitantly with other drugs, including short-acting beta-2 agonists, methylxanthines, and intranasal corticosteroids, commonly used in patients with asthma or COPD, without adverse drug reactions. No formal drug interactions studies have been performed with Advair Diskus.

Drug interactions are uncommon when bronchodilators are given by inhalation. Most interactions seen with these drugs occur when they are given as vasopressors, not bronchodilators.

Fluticasone is a substrate of cytochrome P450 3A4. A drug interaction study with fluticasone aqueous nasal spray in healthy subjects has shown that ritonavir can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations. During post marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing syndrome and adrenal suppression. Therefore, co administration of fluticasone and ritonavir is not recommended unless the potential benefit tot the patient outweighs the risk of systemic corticosteroid side effects.

Adverse Drug Events[35,74-76]

The inhaled treatments for respiratory diseases are generally well tolerated, when used appropriately. Little differences exist in adverse events when comparing albuterol and ipratropium separately, to those of the combination. Table 30 compares the adverse event profiles of the individual drugs (i.e., albuterol and ipratropium) versus Combivent and DuoNeb. Adverse effects are also reported for Advair.

Table 30. Common Adverse Events (%), by System

Adverse Event	Albuterol	Ipratropium	Combivent	DuoNeb	Advair 250/5
Body as a Whole					
Headache	6.6	3.9	5.6	N/A	12
Pain	1.2	1.9	2.5	1.3	NA
Chest Pain	2.9	1.4	0.3	2.6	NA
Influenza	2.9	2.2	1.4	N/A	4
Digestive System					
Nausea	2.6	2.5	2.0	1.4	6
Dyspepsia	0.9	1.1	N/A	1.3	NA
Respiratory System (lower)					
Bronchitis	17.9	12.4	12.3	N/A	2
Dyspnea	4.0	3.9	4.5	N/A	NA
Coughing	2.6	2.8	4.2	N/A	3
Pneumonia	0.6	2.5	1.4	1.3	NA
Bronchospasm	1.7	3.9	0.3	✔	NA

Respiratory System (upper)					
URI	13	12.7	10.9	✔	21
Pharyngitis	2.3	3.3	2.2	4.4	10
Sinusitis	0.9	1.9	2.3	✔	4
Rhinitis	2.3	2.5	1.1	N/A	NA
Other					
Urinary tract infection	N/A	N/A	✔	1.6	NA
Voice alterations	N/A	N/A	N/A	>1	NA
Taste perversion	✔	✔	✔	✔	NA

N/A Incidence not available
✔ Adverse event reported; specific percentages not available

Dosing and Administration[35,74-76]

Tables 31 and 32 describe dosing for the sympathomimetic combination products.

Table 31. Dosing and Administration[35,74-76]

	Availability	Dose /Frequency/Duration
Combivent Aerosol for oral inhalation	90 micrograms albuterol / 18 micrograms ipratropium, per metered spray	Two inhalations, 4 times daily • Maximum number of inhalations in 24 hours is 12. • It is recommended to "test spray" three times before using for the first time and in cases where the aerosol has not been used for more than 24 hours.
DuoNeb Solution for nebulization	2.5mg albuterol / 0.5mg ipratropium per 3ml vial • Supplied in cards of five vials in a foil pouch, in cartons of twenty-five vials	One 3ml vial administered 4 times daily via nebulization • Up to 2 additional 3ml doses allowed per day, if needed.
Advair	Powder for inhalation • 100mcg fluticatsone/50mcg salmeterol • 250mcg fluticatsone/50mcg salmeterol • 500mcg fluticatsone/50mcg salmeterol	Adults and children ≥ 12 years of age - One inhalation twice daily. • 100 mcg/50 mcg twice daily is recommended for patients who are not currently on an inhaled corticosteroid and whose disease severity warrants treatment with 2 maintenance therapies, including patients on non-corticosteroid maintenance therapy. • Please refer to table 10 if patient currently prescribed an inhaled corticosteroid:

Table 32. Recommended Starting Doses of Fluticasone Propionate/Salmeterol for Patients Taking Inhaled Corticosteroids

Current daily dose of inhaled corticosteroid		Recommended strength and dosing schedule of Advair
Beclomethasone dipropionate	≤ 420 mcg 462-840 mcg	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily
Budesonide	≤400 mcg 800-1200 mcg 1600 mcg[1]	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily 500 mcg/50 mcg twice daily
Flunisolide	≤1000 mcg 1250-2000 mcg	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily
Fluticasone propionate inhalation aerosol	≤176 mcg 440 mcg 660-880 mcg[1]	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily 500 mcg/50 mcg twice daily
Fluticasone propionate inhalation powder	≤200 mcg 500 mcg 1000 mcg[1]	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily 500 mcg/50 mcg twice daily

Triamcinolone acetonide	≤1000 mcg 1100-1600 mcg	100 mcg/50 mcg twice daily 250 mcg/50 mcg twice daily

Comparative Effectiveness

The two main factors to be considered when comparing the combination COPD therapies to their monotherapy alternatives are 1) efficacy and 2) compliance. Tables 33, 34, and 35 report results from three that support use of combination ipratropium/albuterol therapy in the treatment of COPD and acute asthma.

Table 33. Combivent Inhalation Aerosol Study Group[78]

Sample	Duration	Results
n=534	12 week	When given albuterol alone, ipratropium alone, or a combination of the two, administered via metered-dose-inhaler: • Peak percent increases in the forced expiratory volume (FEV1) over baseline on the four test days were 31-33% for the combination, 24-25% for ipratropium, and 24-27% for albuterol. These differences were statistically significant. • The $AUC_{0\text{-}4\ hrs}$ means for the combination were 21-44% greater than the ipratropium means and 30-46% greater than the albuterol means. Therefore, the advantage of the combination is apparent primarily during the first 4 hours after administration. • Similar results were noted in the forced vital capacity curves, however, symptom scores did not change over time and did not differ among treatment groups. • Availability of the combination treatment should help improve patient compliance.

Table 34. Canadian Combivent Study Group[79]

Sample	Duration	Results
n=342 patients with acute asthma and a FEV1 <70% of predicted	45-90 minutes	When given a single treatment with 3mg salbutamol (albuterol) sulfate alone, versus 3mg salbutamol (albuterol) sulfate plus 0.5mg ipratropium: • Both treatment arms improved significantly. • The increase in FEV1 in the combination group was 0.61L and in the salbutamol alone group was 0.52L at 90 minutes. • There was a trend toward greater bronchodilation in the combination group, but it was not statistically significant. • Fewer hospitalizations, 5.9% versus 11.2%, occurred in the combination group, but again, was not statistically significant.

Table 35. Combivent Inhalation Solution Study Group[80]

Sample	Duration	Results
n=652 patients with moderate to severe COPD	85 days	When comparing the long-term safety and efficacy of the combination ipratropium and albuterol inhalation solution with that of each separate component: • The acute spirometric response and evening peak expiratory flow rate (PEFR) values with the combination therapy were statistically significantly better compared to albuterol or ipratropium alone. • The quality of life scores, physician global evaluations, symptom scores, and morning PEFR scores were unchanged over the duration of the study in all treatment groups. • There was no significant difference in adverse events in the three treatment groups.

Additional randomized, placebo controlled trials have measured the efficacy of the combination products for the treatment of COPD and asthma. Table 36

summarizes additional outcomes data from recent trials that have undertaken the challenge of determining the relevance of the combination treatments.

Table 36. Additional Outcomes Evidence for Combination Treatment of COPD

Study	Sample	Duration	Results
Albuterol plus ipratropium in prehospital treatment[81]	n=371 patients with reactive airway disease	Retrospective-6 months before and 6 months after institution of an ipratropium protocol	Pre-hospital and ER medical records were examined and compared with the addition of the ipratropium protocol (ipratropium was added to all nebulized treatments with albuterol): ♦ There were no statistically significant differences between groups with regard to change in HR, respiratory rate, or oxygen saturation. ♦ There were also no differences in the proportion of patients with clinical improvement or deterioration as assessed by paramedics. ♦ The only significant change in admission rates from the ER were in patients using a metered-dose inhaler at the time of the illness.
Nebulized salbutamol with and without ipratropium in acute asthma[82] *Study was performed in New Zealand	N=388 patients with asthma, age 18-55 years	Single-dose study	This study was performed to evaluate whether nebulized ipratropium plus salbutamol (Combivent)* confers additional bronchodilation over salbutamol alone: ♦ The mean absolute difference in FEV1 at 90 minutes for Combivent compared to salbutamol was 113ml (SEM +/- 48ml, $p<0.05$). ♦ Independent of the study drug received, a poor response to treatment was predicted by frequent use of an inhaled beta-agonist before presentation ($p<0.0001$), severity of the attack ($p<0.05$), and longer duration of the attack ($p<0.05$). ♦ Patients who had taken more than 10 puffs of inhaled beta-agonist through a metered-dose inhaler or who had serum salbutamol levels of greater than 2mm/L on presentation demonstrated no benefit from the addition of ipratropium. ♦ A single dose of Combivent confers additional bronchodilation over salbutamol alone ($p<0.05$) in acute asthma. ♦ Patients who exhibited the most benefit from addition of ipratropium were those who had consumed the least inhaled beta-agonist before presentation, not those with the most severe asthma.
Addition of ipratropium to nebulized albuterol in children with an acute asthmatic episode[83]	Not available	Single-dose study	When ipratropium was added to nebulized albuterol for infants and children with mild-moderate asthma presenting to a pediatric office: ♦ There were no significant differences between the albuterol group and the combined albuterol / ipratropium group in the relief of respiratory distress, disposition of the patients from the office, or in the incidence of relapse.
Comparison of the effects of salbutamol and ipratropium on exercise endurance in patients with COPD[84] **Study was performed in Japan	n=67 stable patients with COPD	Single-dose of either salbutamol, ipratropium, or placebo prior to endurance testing	When given salbutamol, ipratropium, or a placebo inhalation prior to cycle endurance tests**: ♦ Both salbutamol and ipratropium significantly improved the endurance time by 29 seconds (15%; $p<0.001$) and 27seconds (14%; $p<0.001$), respectively, in comparison with placebo. ♦ The difference in the endurance time between therapy with salbutamol and placebo was significantly, but moderately, related to the difference between therapy with ipratropium and placebo. ♦ There were no relationships, or only weakly significant relationships, between the change in FEV1 and the change in the endurance time, the highest oxygen uptake, and the highest minute ventilation for both salbutamol and ipratropium.

Additionally, multiple studies have reported improved outcomes for patients with asthma or COPD when fluticasone plus salmeterol are compared to monotherapy with fluticasone or salmeterol.[85-90] It is thought that separate but complimentary actions of each agent may explain the beneficial effects of combination therapy.

However, when Advair was compared to concurrent therapy with fluticasone + salmeterol, similar outcomes were seen.[73]

Conclusions

While combination therapy (i.e., albuterol/ ipratropium or fluticasone/salmeterol) has both been shown to improve outcomes in patients with asthma or COPD, there is no data to support a combination product is superior to using separate therapies concurrently.

All brand products within the sympathomimetic combination class reviewed are comparable to generics and offer no significant clinical advantage over other alternatives in general use.

Recommendations

No brand sympathomimetic combination product is recommended for preferred status.

Unclassified Therapeutic Agents/Leukotriene Modifiers (AHFS Class #920000)

I. Comparative Indications [91,92]

In September 1996, the FDA approved Astra-Zeneca's Accolate (Zafirlukast) for the treatment of asthma. This was the first new class of therapeutic agents introduced in 20 years for the treatment of asthma. In February 1998, the FDA approved Merck's Singulair (Montelukast). Zafirlukast and montelukast are leukotriene receptor antagonists. A leukotriene formation inhibitor, Abbott's Zyflo (Zileuton) was approved by the FDA in 1997. These leukotriene modifier agents reduce bronchoconstriction and abnormal mucus production and improve airflow.

Table 38 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 38. Leukotriene Modifiers in this Review

Generic Name	Brand Name Example(s)	FDA Approved Indications
Zafirlukast	Accolate	Asthma: Prophylaxis and chronic treatment of asthma in adults and children ≥ 5 years of age
Montelukast sodium	Singulair	Asthma: Prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older. Seasonal allergic rhinitis: Relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older.
Zileuton	Zyflo	Asthma: Prophylaxis and chronic treatment of asthma in adults and children ≥ 12 years of age.

*No products are currently generically available

II. Pharmacokinetics[91,92]

There are two types of leukotriene modifiers, leukotriene receptor antagonists and leukotriene formation inhibitors. Zafirlukast and montelukast sodium are leukotriene receptor antagonists. Zafirlukast is a selective and competitive leukotriene receptor antagonist (LTRA) of leukotriene D_4 and E_4 (LTD_4 and LTE_4). Montelukast is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene ($CysLT_1$) receptor. It binds with high affinity and selectivity to the $CysLT_1$ receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or beta-adrenergic receptor). Montelukast inhibits physiologic actions of LTD_4 at the $CysLT_1$ receptor without any agonist activity. Zileuton is a specific inhibitor of 5-lipoxygenase and thus inhibits leukotriene (LTB_1, LTC_1, LTD_1 and LTE_1) formation.

Table 39 compares pharmacokinetic parameters for the leukotriene modifiers.

Table 39. Leukotriene Modifier Pharmacokinetic Comparison

Parameter	Zafirlukast	Montelukast	Zileuton
Bioavailability	NA	58-66% (oral tablets) 73% (chewable tablets)	NA
Peak Plasma Level	3 hours	3-4 hours	1.7 hours
Protein Binding	99%	99%	93%
Food & Absorption	Reduces absorption by approximately 40%	Absorption not affected by food	Can be administered with or without food
Metabolism	CYP2C9 & CYP3A4	CYP2C9 & CYP3A4	CYP1A2, CYP2C9 & CYP3A4
Half Life	10 hours	2.7 - 5.5 hours	2.5 hours

*NA=Not available

III. Drug Interactions[91,92]

There are no clinically significant (level or 2) drug interactions for any of the leukotriene modifiers.

The following drugs may have a drug interaction with montelukast: phenobarbital, prednisone and rifampin. The following drugs did not have a drug interaction with montelukast: digoxin, ethinyl estradiol, levonorgestrel, medroxyprogesterone, mestranol, norethindrone, norgestrel, prednisolone, terfenadine, theophylline and warfarin.

The following drugs may have a drug interaction with zafirlukast: aspirin, dofetilide, erythromycin, erythromycin/sulfamethoxazole, terfenadine, theophylline and warfarin.

The following drugs may have a drug interaction with zileuton: astemizole, beta- adrenergic blocking agents, ergot derivatives, naproxen, pimozide, terfenadine, theophylline and warfarin.

IV. Adverse Drug Events[91,92]

Table 40 includes report adverse drug events for the leukotriene modifiers.

Table 40. Leukotriene Modifier vs. Placebo Adverse Drug Events

Adverse Drug Event	Montelukast	Placebo	Zileuton	Placebo	Zafirlukast	Placebo
Headache	18.4%	18.1%	24.6%	24%	12.9%	11.7%
Dizziness	1.9%	1.4%			1.6%	1.5%
Abdominal Pain	2.9%	2.5%	4.6%	2.4%	1.8%	1.1%
Dyspepsia	2.1%	1.1%	8.2%	2.9%	1.3%	1.2%
Nausea			5.5%	3.7%	3.1%	2.0%
Diarrhea					2.9%	2.1%
Vomiting					1.5%	1.1%
GI Infections	1.5%	0.5%				
ALT Increased	2.1%	2%	12%	0.2%	1.5%	1.1%
AST Increased	1.6%	1.2%				
Leukopenia			1%	0.6%		
Pyuria	1%	0.9%				
Influenza	4.2%	3.9%				
Cough	2.7%	2.4%				
Congestion, nasal	1.6%	1.3%				
Asthenia, Fatigue	1.8%	1.2%	3.8%	2.4%	1.8%	1.6%
Dental Pain	1.7%	1%				
Pain			7.8%	5.3%	1.9%	1.7%
Myalgia			3.2%	2.9%	1.6%	1.5%
Rash	1.6%	1.2%				
Fever	1.5%	0.9%			1.6%	1.1%
Trauma	1%	0.8%	3.4%	2%	1.6%	1.5%

Reduction of systemic corticosteroid doses in patients taking a leukotriene modifier (including montelukast) has been associated with Churg-Strauss syndrome. A causal relationship has not been identified between the reaction and leukotriene antagonists, but careful monitoring is recommended when steroid doses are reduced in patients taking a leukotriene antagonist.

V. Dosing and Administration[91,92]

Table 41 includes recommended doses for each of the leukotriene modifiers.

Table 41. Leukotriene Modifier Dosages

Drug	Dosage
Montelukast	**Adults and adolescents 15 years of age and older:** One 10 mg tablet daily. **Children 6 to 14 years of age:** One 5 mg chewable tablet daily.

	Children 2 to 5 years of age: One 4 mg chewable tablet or one 4 mg oral granule packet daily. **Children 12 to 23 months of age with asthma:** One packet of 4 mg granules daily taken in the evening.
Zafirlukast	**Adults and children ≥ 12 years of age:** The recommended dose of zafirlukast is 20 mg twice daily. **Children 5 to 11 years of age:** The recommended dose of zafirlukast is 10 mg twice daily. Because food reduces bioavailability of zafirlukast, take ≥ 1 hour before or 2 hours after meals.
Zileuton	The recommended dosage of zileuton for the symptomatic treatment of patients with asthma is one 600 mg tablet 4 times a day for a total daily dose of 2400 mg. For ease of administration, zileuton may be taken with meals and at bedtime.

VI. Effectiveness

There are no head to head trials that directly compare the leukotriene modifiers.

Montelukast (Singulair)

Chronic Asthma:

1. In a double-blind trial the mean inhaled corticosteroid dose was reduced by 47% in patients with STABLE ASTHMA on montelukast. More patients on montelukast (40%) than on placebo (29%) completely tapered off inhaled corticosteroids[93].
2. In a multicenter, randomized, parallel-group study, concomitant treatment with montelukast provided improved asthma control in patients (15 years and older) who had INTERMITTENT or PERSISTENT ASTHMA symptoms despite inhaled corticosteroid therapy that was comparable to 400 to 500 micrograms (mcg) of beclomethasone[94].
3. In a 12-week, randomized, multicenter, double-blind, placebo-controlled study (n=681), montelukast 10 milligrams (mg) once daily at bedtime significantly improved overall asthma control and was well tolerated[95].
4. Short-term, placebo-controlled study (chronic asthma; 200 milligrams three times daily, 11 days); significant improvement in FEV-1 (day 1, 11), reduction in daily beta-agonist use, improvement in daytime asthma symptoms (benefits observed irrespective of concurrent use of inhaled corticosteroids)[96].
5. Chronic asthma, placebo-controlled study (n=681; current treatment not specified but FEV-1 improved more than 15% with beta-agonist pre treatment; 10 milligrams once daily for 12 weeks). Montelukast group required fewer corticosteroid rescues (7% versus 10%); had fewer (mean) asthma exacerbation days (10.7% versus 15.5%); and had more (mean) asthma-free days (37% versus 27%) (p less than 0.001)[97].

Allergic Rhinitis

In a double-blind multicenter trial monotherapy with either montelukast or loratadine provided limited benefit for symptoms of allergic rhinitis; however, concomitant montelukast plus loratadine provided relief of symptoms and nighttime symptoms improved within the first day of concomitant therapy[98].

Zafirlukast (Accolate)

Asthma:

1. Oral zafirlukast has shown to be superior to placebo in the treatment of mild-to-moderate asthma in randomized studies up to 13 weeks in duration[98-101]. Zafirlukast reduces the risk of asthma exacerbation and the need for rescue therapy during asthma exacerbation[102].
2. In a pooled data analysis of 5 double-blind, multicenter, randomized, placebo controlled, 13 week trials in steroid-naive patients with mild to moderate asthma Zafirlukast, 20 milligrams twice daily, reduced the risk of asthma exacerbation by almost 50%. Zafirlukast reduced the requirement for rescue therapy (oral corticosteroids and additional asthma treatment, other than beta-agonist) by approximately 50% during an asthma exacerbation[103].
3. Addition of high-dose zafirlukast to the inhaled corticosteroid treatment regimen of patients whose asthma was not adequately controlled by corticosteroids improved pulmonary function, alleviated asthma symptoms, decreased the need for beta-2 agonists, and reduced the frequency of asthma exacerbations[104].
4. In a 6-week, double-blind, randomized, placebo-controlled trial, zafirlukast maintained effectiveness in the long-term (39 to 52 weeks) for patients with mild asthma[105].

Zileuton (Zyflo)

Asthma:

1. Compared to placebo, zileuton 600 milligrams (mg) four times daily resulted in statistically significantly fewer exacerbations of asthma requiring oral corticosteroids, decreased need for beta-agonist therapy, decreased symptoms associated with asthma, and improved pulmonary function test values. This was a 3-month study, which enrolled 401 patients who met the American Thoracic Society criteria for asthma and received only as-needed beta-agonists[106].
2. In placebo-controlled trial of 272 assessable patients with mild to moderate asthma a 6-month treatment course of zileuton was proven to be safe and effective in the treatment of asthma; improving both objective and subjective asthma outcome parameters. It appears that the zileuton 600 milligram (mg)-dose is more effective than the 400 mg-dose[107].
3. In a double-blind, placebo-controlled study involving 139 patients with mild-to-moderate asthma and an earlier study by Israel et al, oral Zileuton was associated with objective improvement in airway function and a significant decrease in asthmatic symptoms. Zileuton 600 milligrams (mg) four times daily resulted in a significant decrease in steroid bursts compared to placebo in patients with moderate stable asthma[108,109].

VII. Conclusions

While leukotriene modifiers are recommended as alternative therapies for the treatment of asthma, one agent is not recommended over another. All brand products within the leukotriene modifier class are comparable to each other in this class and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand leukotriene modifier product is recommended for preferred status.

Respiratory Mast Cell Stabilizers (AHFS Class 920000)

I. Comparative Indications [110,111]

At one time a first choice for treatment of asthma in children, mast cell stabilizers have become a second line treatment being replaced by inhaled corticosteroids. They are alternatives in treating mild persistent chronic asthma. These agents, cromolyn sodium (Intal) and nedocromil (Tilade), must be administered before exposure to an allergen to prevent development of the allergic event. Because these drugs do not pass the cell membrane, they do not exert a systemic action and are virtually not metabolized. To be affective either drug must be applied topically. Both products are highly effective in patients who have IgE-mediated allergic rhinitis.

Table 42 lists the products included in this review. This review encompasses all dosage forms and strengths.

Table 42. Mast Cell Stabilizer Products in this Review

Generic Name	Brand Name Example(s)	FDA Approved Indications
Cromolyn Sodium	Intal	Bronchial Asthma – Adults and children ≥ 2years of age (nebulizer) or ≥ 5 years of age (aerosol) Bronchospasm Prophylaxis – Adults and children ≥2years of age (nebulizer) or ≥ 5 years of age (aerosol) Mastocytosis
Nedocromil Sodium	Tilade	Asthma – Maintenance therapy in the management of adult and pediatric patients ≥ 6 years of age with mild to moderate asthma

II. Pharmacology and Pharmacokinetics[110,111]

Cromolyn inhibits the degranulation of sensitized mast cells that occurs after exposure to specific antigens. Cromolyn acts by inhibiting the release of histamine and SRS-A (slow-reacting substance of anaphylaxis) from the mast cell. Another activity demonstrated in vitro is the capacity of cromolyn to inhibit the degranulation of non-sensitized rat mast cells by phospholipase A and the subsequent release of chemical mediators. In another study, cromolyn did not inhibit the enzymatic activity of released phospholipase A on its specific substrate. Cromolyn has no intrinsic vasoconstrictor, antihistaminic or anti-inflammatory activity.

Nedocromil inhibits the in vitro activation of, and mediator release from, a variety of inflammatory cell types associated with asthma (e.g., eosinophils, neutrophils, macrophages, mast cells, monocytes, platelets). In vitro, nedocromil inhibits the release of mediators (e.g., histamine, leukotriene C_4, prostaglandin D_2). Similar studies with human bronchoalveolar cells showed inhibition of histamine release from mast cells and beta-glucuronidase release from macrophages. Nedocromil inhibits the development of early and late bronchoconstriction responses to inhaled antigens. The development of airway hyper-responsiveness to nonspecific bronchoconstrictors also was inhibited. Nedocromil reduced antigen-induced

increases in airway microvasculature leakage when administered IV. The drug acutely inhibits the bronchoconstrictor response to several kinds of challenge. Pretreatment with single doses inhibited the bronchoconstriction caused by sulfur dioxide, inhaled neurokinin A, various antigens, exercise, cold air, fog, and adenosine monophosphate. Nedocromil has no bronchodilator, antihistamine, or corticosteroid activity, and when delivered by inhalation at the recommended dose, has no known systemic activity.

Table 43 includes pharmacokinetic parameters for mast cell stabilizers.

Table 43. Mast Cell Stabilizer Pharmacokinetic Parameter Comparison

Parameter	Cromolyn Sodium	Nedocromil Sodium
Peak Plasma Level	Cromolyn is topically active and serum concentrations cannot be equated with drug concentrations at the active sites.	20 – 28 minutes Following a 4-mg inhaled dose of nedocromil in healthy volunteers, mean peak levels were 3.3 ng/mL, followed by a plateau for approximately 1 hour, then a monoexponential decline in plasma levels.
Protein Binding	63% - 76%	89%
Metabolism	Drug is not metabolized	Drug is not metabolized
Half Life	80-90 minutes	1.5 – 3.3 hours

III. Drug Interactions[110,111]

There are no reported drug interactions for either Cromolyn Sodium or Nedocromil Sodium. Because the drug is not metabolized and must have a topical application there is little chance for a drug interaction to occur.

IV. Adverse Drug Events[110,111]

Cromolyn Sodium

The most frequently reported adverse reactions attributed to cromolyn sodium (on the basis of recurrence following readministration) involve the respiratory tract and include bronchospasm (sometimes severe, associated with a precipitous fall in pulmonary function [FEV_1]), cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation, and wheezing.

Aerosol: Throat irritation or dryness; bad taste; cough; wheeze; nausea.
CNS: Dizziness; headache.
GU: Dysuria; urinary frequency.
Hypersensitivity: Anaphylaxis; rash; urticaria; angioedema.
Special senses: Lacrimation; swollen parotid gland.
Miscellaneous: Joint swelling and pain; substernal burning; myopathy; pulmonary infiltrates with eosinophilia.
CNS: Vertigo; drowsiness.
Dermatologic: Exfoliative dermatitis; photodermatitis.
Musculoskeletal: Myalgia; polymyositis.
Respiratory: Hemoptysis; sneezing; nasal itching; nasal bleeding; nasal burning.
Miscellaneous: Stomachache; anemia; hoarseness; nephrosis; liver disease; serum sickness; periarteritic vasculitis; pericarditis; peripheral neuritis.

Inhalation solution:
Miscellaneous*:* Cough; nasal congestion; wheezing; sneezing; nausea; drowsiness; nasal itching; epistaxis; nose burning; serum sickness; stomachache.

Nedocromil

Nedocromil is generally well tolerated. Of the 4,400 patients who received 2 inhalations of nedocromil 4 times/day, 2,632 were in placebo-controlled, parallel trials. Of these, 6% withdrew from the trials because of adverse events, compared with 5.7% of the 2446 patients who received placebo. The reasons for withdrawal were generally similar in the nedocromil and placebo-treated groups, except that patients withdrew because of bad taste statistically more frequently on nedocromil than on placebo. Headache reported as severe or very severe, some with nausea and ill feeling, was experienced by 1% of nedocromil patients and 0.7% of placebo patients.

Table 44. Nedocromil Adverse Drug Events

Adverse reaction	% Experiencing adverse reaction		% Withdrawing	
	Nedocromil (N = 2632)	Placebo (N = 2402)	Nedocromil	Placebo
GI				
Nausea[1]	3.9	2.3	1.1	0.5
Vomiting[1]	2.5	1.6	0.2	0.3
Abdominal pain[1]	1.9	1.3	0.2	0.1
Dyspepsia	1.5	1.1	0.1	0.1
Diarrhea	1.3	1.2	0.1	0
Respiratory				
Coughing	8.9	10.2	1.1	1.2
Bronchospasm[2]	8.4	11.8	1.4	2
Pharyngitis	7.6	7.5	0.5	0.4
Rhinitis[1]	7.3	6	0.1	0.1
Upper respiratory infection	6.7	6.3	0.1	0.2
Sinusitis	3.3	4.1	1.1	0
Dyspnea	2.5	3.3	0.8	1
Sputum increased	1.5	1.4	0.1	0.2
Bronchitis	1.1	1.5	0.1	0.1
Respiratory disorder	0.8	1.1	0	0
Miscellaneous				
Unpleasant taste[1]	11.6	3.1	1.6	0
Headache	8.1	7.5	0.4	0.2
Chest pain	3.6	3.8	0.7	0.5
Fever	3.1	3.7	0.1	0.1
Viral infection	2.4	3.2	0.1	0.1
Conjunctivitis	1.1	0.7	0	0.1
Fatigue	1	0.8	0.2	0
Dizziness	0.8	1.3	0.1	0.2
Rash[2]	0.5	1.2	0.1	0

[1]Statistically significantly higher frequency on nedocromil (**P** < 0.05).
[2]Statistically significantly higher frequency on placebo (**P** <0.05).

Miscellaneous:
Arthritis; tremor; sensation of warmth(less than 1%).

In clinical trials with 2632 patients receiving nedocromil, 2 patients(0.08%) developed neutropenia and 3 patients (0.11%) developed leukopenia. Although it is unclear if these

reactions were caused by nedocromil, in several cases these abnormal laboratory tests returned to normal when nedocromil was discontinued.

There have been reports of clinically significant elevation of hepatic transaminases (ALT and AST greater than 10 times the upper limit of the normal reference range in 1 patient) associated with the administration of nedocromil. It is unclear if these abnormal laboratory tests in asymptomatic patients were caused by nedocromil.

Postmarketing:

Cases of bronchospasm immediately following dosing with nedocromil have been reported. Isolated cases of pneumonitis with eosinophilia (PIE syndrome)and anaphylaxis also have been reported in which a relationship to the drug is undetermined.

V. Dosing and Administration[110,111]

Cromolyn Sodium:

Asthma:

Metered Dose Inhaler - usual starting dose for adults and children ≥ 5 years of age is 2 metered sprays (800 micrograms/spray) from the metered-dose inhaler inhaled 4 times daily at regular intervals. To prevent bronchospasm from exercise, exposure to cold air, or environmental agents, the usual dose is 2 metered sprays (800 micrograms/spray) inhaled shortly before encountering the precipitating factor, but not more than 60 minutes before.

Nebulizer Solution for Inhalation - the recommended starting dose for adults and children ≥ 2 years of age is 20 milligrams (the contents of one 2-mL ampule) administered 4 times daily at regular intervals using a power-operated nebulizer. To prevent bronchospasm from exercise, exposure to cold air, or environmental agents, the usual dose is 20 milligrams administered using a power-operated nebulizer shortly before encountering the precipitating factor, but not more than 60 minutes before.

Nedocromil Sodium:

Asthma:

Inhalation - The recommended dose of nedocromil in adults and children ≥ 6 years of age is 2 puffs four times a day.

VI. Effectiveness

There are no head to head trials comparing the two mast cell stabilizers.

Cromolyn is useful in the prophylactic management of asthma. If improvement occurs, it will ordinarily occur within the first 2 to 4 weeks of administration, as manifested by a decrease in the severity of clinical symptoms of asthma, or in the need for concomitant therapy, or both[112]. Numerous studies have reported the efficacy of cromolyn in adults and children with asthma, producing success rates

ranging from 60 to 90%[113-122]. The clinical effects of cromolyn are directly related to penetration of the drug into the small airways[123-126].

Inhaled nedocromil was effective in the treatment of bronchial asthma in a 6-week multicenter, double-blind trial involving 167 patients[127]. Nedocromil was effective in improving asthma control in adult asthmatics not optimally controlled on bronchodilator therapy alone[128]. In this 3-month double-blind study, nedocromil 4 milligrams twice daily by metered-dose inhaler was added to oral or inhaled bronchodilator therapy. Significant improvements in nighttime asthma, daytime asthma, cough, daytime bronchodilator use, and forced expiratory volume were observed during the study, although these differences did not always reach statistical significance. Bronchodilator use was reduced throughout the study and was statistically significant during the first 4 weeks of treatment. Concomitant nedocromil allowed the reduction of bronchodilator dose in many studies. Both day and night bronchodilator therapy could be reduced (not always significantly) in many of these studies, with further clinical improvement noted[129-131].

VII. Conclusions

While mast cell stabilizers are recommended as alternative therapies for the treatment of asthma, one agent is not recommended over another. All brand products within the mast cell stabilizer product class are comparable to each other and to generics in this class and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand mast cell stabilizer is recommended for preferred status.

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Appendix 1. Stepwise Treatment Approach for Managing Asthma in Adults and Children Older than 5 Years of Age[4]

Classify Severity: Clinical Features Before Treatment of Adequate Control	Symptoms/Day Symptoms/Night	PEF or FEV_1 PEF Variability	Medications Required to Maintain Long-Term Control
Step 4 **Severe Persistent**	Continual Frequent	Less than or equal to 60% > 30%	**Preferred Treatment:** High-dose inhaled corticosteroids AND Long-acting inhaled $beta_2$ agonists AND, if needed: Systemic corticosteroids
Step 3 **Moderate Persistent**	**Daily** >1 night/week	>60% to <80% >30%	**Preferred Treatment:** Low to medium dose inhaled corticosteroids and long-acting inhaled $beta_2$ agonists Alternative treatment (listed alphabetically): Increase inhaled corticosteroids within medium dose range OR Low to medium dose inhaled corticosteroids and either leukotriene modifier or theophylline. OR, in those with recurring severe exacerbations: Increase inhaled corticosteroids within medium-dose range and add long-acting inhaled $beta_2$ agonist or a leukotriene modifier or theophylline
Step 2 **Mild Persistent**	➢ 2/week but <1 x/day ➢ >2 nights/month	Greater than or equal to 80% 20%-30%	**Preferred Treatment:** Low-dose inhaled corticosteroids Alternative Treatment (listed alphabetically): Cromolyn, leukotriene modifier, nedocromil, OR sustained theophylline to serum concentration of 5-15 mcg/mL
Step 1 **Mild Intermittent**	Less than or equal to 2 days/week Less than or equal to 2 nights/month	Greater than or equal to 80% <20%	No daily medication needed Severe exacerbations may occur, separated by long periods of normal lung function and no symptoms. A course of systemic corticosteroids is recommended.
Step down: Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible			Step up: If control is not maintained, consider step-up. First, review patient medication technique, adherence, and environmental control.

Appendix 2. Stepwise Treatment Approach for Managing Infants and Young Children (5 Years of Age and Younger) with Acute or Chronic Asthma [4]

Classify Severity: Clinical Features Before Treatment of Adequate Control	Symptoms/Day Symptoms/Night	Medications Required to Maintain Long-Term Control
Step 4 **Severe Persistent**	Continual Frequent	**Preferred Treatment:** High-dose inhaled corticosteroids AND Long-acting inhaled $beta_2$ agonists AND, if needed: Systemic corticosteroids
Step 3 **Moderate Persistent**	**Daily** >1 night/week	**Preferred Treatment:** Low dose inhaled corticosteroids and long-acting inhaled $beta_2$ agonists OR medium dose inhaled corticosteroids Alternative treatment: Low dose inhaled corticosteroids and either leukotriene modifier or theophylline OR, in those with recurring severe exacerbations: Medium dose inhaled corticosteroids and long-acting inhaled $beta_2$ agonist Alternate treatment: Medium dose inhaled corticosteroids and either leukotriene modifier or theophylline
Step 2 **Mild Persistent**	➢ 2/week but <1 x/day ➢ >2 nights/month	**Preferred Treatment:** Low-dose inhaled corticosteroids Alternative Treatment: Cromolyn, or leukotriene modifier
Step 1 **Mild Intermittent**	Less than or equal to 2 days/week Less than or equal to 2 nights/month	No daily medication needed
Step down: Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible		Step up: If control is not maintained, consider step-up. First, review patient medication technique, adherence, and environmental control.

Appendix 3. Therapy at Each Stage of COPD[7]

Old	**0: At Risk**	**I: Mild**	**II: Moderate** **IIA**	**IIB**	**III: Severe**
New	**0: At Risk**	**I: Mild**	**II: Moderate**	**III: Severe**	**IV: Very Severe**
Characteristics	♦ Chronic symptoms ♦ Exp. to risk factors ♦ Normal Spirametry	♦ FEV1/ FVC<70% ♦ FEV1≥ 80% ♦ With or without symptoms	♦ FEV1/FVC<70% ♦ 50%≤ FEV1<80% ♦ With or without symptoms	♦ FEV1/FVC<70% ♦ 30%≤ FEV1 <50% ♦ With or without symptoms	♦ FEV1/FVC<70% ♦ FEV1<30% or FEV1<50% predicted plus chronic respiratory failure
	Avoidance of risk factors; influenza vaccination				
		Add short-acting bronchodilator when needed			
			Add regular treatment with one or more long-acting bronchodilators and **Add** rehabilitation		
				Add inhaled glucocorticosteroids if repeated exacerbations	
					Add long-term oxygen if chronic respiratory failure and consider surgical treatments

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
Antiarrhythmic Agents (AHFS Class 240404)
March 24, 2004

I. Overview

Antiarrhythmic drugs have specific electrophysiologic actions that alter cardiac conductions. These mechanisms usually form the basis for the grouping of these agents into specific categories based on their electrophysiologic mechanisms.[1] Vaughan Williams first proposed the most frequently used classification system. Research in recent years has provided extensive data regarding the cellular mechanisms by which some of the antiarrhythmic drugs act, however, the general approach to antiarrhythmic therapy remains largely empirical. [1] All of the antiarrhythmic drugs act by altering ion fluxes within the excitable tissues within the heart. The three primary ions of primary importance are Na+, Ca++, and K+.[2] Finally, recent results of several clinical trails, including the Cardiac Arrhythmia Suppression Trial (CAST), have indicated that many antiarrhythmic agents, in particular the class I agents, may significantly increase mortality rates when compared to placebo.[3] This review encompasses all dosage forms and strengths. Table 1 includes those antiarrhythmics included in this review and their respective Vaughan Williams Classification .

Table 1. Antiarrhythmic Products in the Review

Generic Name	Example Brand Name(s)	Vaughan Williams Classification
Amiodarone	Cordarone	III
Disopyramide	Norpace, Norpace CR	Ia
Dofetilide	Tikosyn*	III
Flecainide	Tambocor	Ic
Mexiletine	Mexitil	Ib
Moricizine	Ethmozine*	I
Procainamide	Procanbid, Pronestyl	Ia
Propafenone	Rythmol	Ic
Quinidine	Quinidex Extentabs (Quinidine sulfate), Quinidine gluconate	Ia
Tocainide	Tonocard	Ib

*These products are currently not available in generic formulations

II. Current Treatment Guidelines

The ACC/AHA has developed guidelines to aid clinicians in determining the most safe and effective options to treat multiple arrhythmias. Nevertheless, there has been a decline in antiarrhythmic drug use as a result of the following: 1. Increased mortality with antiarrhythmic agents as observed in clinical trials (e.g., CAST). 2. Risk of serious side effects with certain antiarrhythmic agents (e.g., Amiodarone: pulmonary fibrosis, optic neuritis; Procainamide: lupus-like syndrome). 3. Advancement in non-pharmacologic therapy (defibrillators, ICDs), which appear superior to antiarrhythmic agents in decreasing mortality in clinical trials.[4]

Considerations in choosing antiarrhythmic therapy should be based on presence of cardiovascular disease as well as type of arrhythmia. In addition, renal or hepatic dysfunction also plays a role in determining which agent is most appropriate.

ATRIAL FIBRILLATION

The AFFIRM trial revealed a trend towards increased mortality and more adverse drug events with antiarrhythmic therapy versus rate control in patients with atrial fibrillation. Digoxin should not be used acutely because of its delayed onset of action. Patients with left ventricular dysfunction should be treated first-line with digoxin. Patients with Wolff-Parkinson White (WPW) syndrome should avoid AV nodal blocking agents. IV Procainamide is the drug of choice in WPW.

Several treatment options can be used to restore and maintain normal sinus rhythm. However, rate control should be targeted first. For hemodynamically unstable patients, control should be achieved with direct current cardioversion (DCC). For patients that are hemodynamically stable, after the heart rate has been control and patient has been properly anticoagulated, then conversion can be achieved with DCC or drug therapy (dofetilide, amiodarone, ibutilide, flecainide, propafenone, or quinidine).[4]

Maintenance of normal sinus rhythm can be treated with antiarrhythmic therapy. For patients with no structural heart disease, the preferred agents are Class IC (flecainide or propafenone) because they are well tolerated with low incidence of organ toxicity and low incidence of proarrhythmias. Sotalol or amiodarone are also viable alternatives. Class IA agents should be avoided unless amiodarone fails or is contraindicated. Patients with underlying heart failure should be treated first-line with amiodarone or dofetilide as an alternative.[4]

ACUTE TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

DCC is the treatment of choice in patients experiencing severe symptoms. Drug therapy is based on arrhythmia and QRS length. IV adenosine is usually the first-line agent. Procainamide may be substituted when the arrhythmia is presumed to be ventricular tachycardia. Intravenous amiodarone may also be used in patients with wide QRS complex and irregular arrhythmias.[4,6]

VENTRICULAR ARRHYTHMIA

Most antiarrhythmics are no longer used due to the increased incidence of fatal ventricular arrhythmias (CAST). For premature ventricular contractions (PVCs), lidocaine was associated with excess mortality despite a decrease in ventricular tachycardia. Patients with post-MI and/or left ventricular ejection fraction ≤ 40% and who are symptomatic may be treated with amiodarone. Amiodarone followed by dofetilide are the agents of choice in patients with sustained ventricular tachycardia/ventricular fibrillation in particular if structural heart disease is present.[7,8]

III. Indications

Table 2 includes indications for the different antiarrhythmics included in this review.

Table 2. Vaughan Williams Classification of Antiarrhythmics and Their Indications[2]

Type	*Generic Name*	*Brand Name(s)*	*Indication*
I	Moricizine	Ethmozine *	VT
Ia	Disopyramide	Norpace, Norpace CR	AF, VT
	Procainamide	Procanbid	AF, AFlutter VT, WPW
	Quinidine	Quinidine Extentabs (Quinidine sulfate)	AF, PSVT, VT, WPW
Ib	Mexiletine	Mexitil *	VT
	Tocainide	Tonocard	VT
Ic	Flecainide	Tambacor	VT, PSVT, AF
	Propafenone	Rythmol	VT, Paroxysmal AF
III	Amiodarone	Pacerone	VT
	Dofetilide	Tikosyn *	AF, Cardioversion AF

AF= Atrial Fibrillation PSVT= Paroxysmal Supraventricular Tachycardia
VT= Ventricular Tachycardia WPW= Wolff-Parkinson White
* Not available in a generic formulation

IV. Pharmacokinetics

Table 3 includes the pharmacokinetic properties for each of the antiarrhythmics.

Table 3. Comparative Pharmacokinetic Properties of Antiarrhythmic Agents[2]

Drug	Bioavailability (%)	*Elimination*	Protein Binding (%)	Half-life	Therapeutic Range (mcg/ml)
Moricizine	34-38	Hepatic	92-95	1-6 h	-
Disopyramide	70-95	Hepatic/Renal	50-80	4-8 h	2-6
Procainamide	75-95	Hepatic/Renal	10-20	2.5-5 h	4-15
Quinidine	70-80	Hepatic	80-90	5-9 h	2-6
Mexiletine	80-95	Hepatic	60-75	6-12 h	0.75-2
Tocainide	90-95	Hepatic	10-30	12-15 h	4-10
Flecainide	90-95	Hepatic/Renal	35-45	12-30 h	0.3-2.5
Propafenone	11-39	Hepatic	85-95	12-32 h	-
Amiodarone	22-28	Hepatic	95-97	15-100 d	1-2.5
Dofetilide	>90	Renal	60-70	10h	-

V. Drug Interactions

(Clinically significant [rated 1 (major) or 2 (moderate)] drug interactions are listed below.)

Moricizine

- Cimetidine increases moricizine by 50%
- Moricizine decreases diltiazem levels

Disopyramide

- Certain macrolides increase disopyramide blood levels; may cause QRS prolongation
- Drugs that prolong the QT interval (quinolones, cisapride, ziprasidone)
- Rifampin may decrease serum levels of disopyramide

Procainamide

- Amiodarone increases procainamide or NAPA levels; consider reducing dose by 25%
- Cimetidine increases serum procainamide concentrations
- Drugs that prolong the QT interval (quinolones, cisapride, ziprasidone)
- Trimethoprim increases procainamide or NAPA blood levels

Quinidine

- CYP3A4 inhibitors (azole antifungals, protease inhibitors) may increase quinidine levels
- Amiodarone, cimetidine, verapamil and diltiazem may increase quinidine levels
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone)
- Codeine: analgesic efficacy is reduced
- May increase digoxin blood levels
- Antacids may increase serum quinidine levels
- Effects of certain beta-blockers will be increased by quinidine
- Non-depolarizing muscle relaxant effects may be enhanced by quinidine
- Amiloride may cause proarrhythmias

Mexiletine

- Decreased plasma levels: phenobarbital, phenytoin and other inducers
- Increased toxicity/levels of caffeine and theophylline

Tocainide

- Decreased plasma levels: phenobarbital, rifampin, phenytoin and other inducers
- Increased effects with metoprolol

Flecainide

- Ritonavir increases flecainide concentrations
- Amiodarone increases flecainide plasma levels; consider reducing dose by 25%

Propafenone

- Certain SSRIs (fluoxetine, paroxetine, fluvoxamine) may increase propafenone serum levels

- Digoxin blood levels are increased
- Rifampin may decrease propafenone blood levels
- Metoprolol, propranolol, and theophylline blood levels may be increased
- Quinidine increases propafenone blood levels
- Ritonavir increases propafenone serum concentrations

Amiodarone

- Protease Inhibitors increase amiodarone levels
- Anticoagulant levels are increased
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone)
- Cyclosporine levels are increased
- Digoxin levels may be increased
- Fentanyl co-administration may result in hypotension, bradycardia, and decreased cardiac output
- Phenytoin concentrations are increased due to reduction in phenytoin metabolism
- Procainamide concentrations may be increased
- Quinidine concentrations may be increased and can cause potentially fatal arrhythmias

Dofetilide

- CYP3A4 inhibitors (azole antifungals, protease inhibitors) may increase dofetilide levels
- Cimetidine inhibits dofetilide elimination
- Drugs that prolong QT interval (quinolones, cisapride, ziprasidone)
- Verapamil causes an increase in dofetilide's plasma levels by 42%
- Renal cationic transport inhibitors such as amiloride may increase dofetilide levels

VI. Adverse Drug Events

Table 4 includes possible adverse drug events associated with antiarrhythmic therapy.

Table 4. Side Effects of Antiarrhythmic Agents[2]

Drug	*Side Effects*
Moricizine	Dizziness, Headache, GI, Aggravation of underlying conduction disturbance or ventricular arrhythmias
Disopyramide	Anticholinergic symptoms, Torsades de Pointes, heart failure, conduction disturbances, ventricular arrhythmias, hypoglycemia
Procainamide	SLE, Torsades de Pointes, aggravation of underlying heart failure, conduction disturbances, agranulocytosis
Quinidine	Cinchonism, diarrhea, hypotension, Torsades de Pointes, conduction disturbances, ventricular arrhythmias, hepatitis, thrombocytopenia, hemolytic anemia
Mexiletine	CNS disturbances, psychosis, conduction disturbances, ventricular arrhythmias
Tocainide	CNS disturbances, psychosis, conduction disturbances, ventricular arrhythmias, rash/arthralgias, pulmonary infiltrates, agranulocytosis, thrombocytopenia
Flecainide	Blurred vision, dizziness, headache, bronchospasm, heart

	failure, conduction disturbances, ventricular arrhythmias
Propafenone	Blurred vision, dizziness, headache, bronchospasm, heart failure, conduction disturbances, ventricular arrhythmias
Amiodarone	CNS disturbances, corneal microdeposits, blurred vision, optic neuropathy/neuritis, ventricular arrhythmias, Torsades de Pointes, bradycardia, AV block, bruising, pulmonary fibrosis, hepatitis, hypo/hyperthyroidism, photosensitivity, blue-gray discoloration, myopathy, hypotension, phlebitis (IV use)
Dofetilide	Torsades de Pointes

VII. Dosing and Administration

Table 5 includes usual doses for the antiarrhythmics included in this rule.

Table 5. Usual Doses for Antiarrhythmic Agents[2]

Drug	*Maintenance Doses*
Moricizine (Ethmozine®)	200-300mg q8h
Disopyramide (Norpace®) Disopyramide CR (Norpace CR®)	100-200mg q6h 200-400mg q12h (controlled-release)
Procainamide (Procan®) Procanamide ER (Procanbid®)	250-750mg q3h 500-100mg q12h (controlled-release)
Quinidine gluconate SR Quinidine sulfate (Quinidine Extentabs®)	324-648mg q8-12h 300-600mg q8-12h
Mexiletine (Mexitil®)	200-300mg q8h
Tocainide (Tonocard®)	400-600mg q8h
Flecainide (Tambacor®)	50-200mg q12h
Propafenone (Rythmol®)	150-300mg q8h
Amiodarone (Cordarone®)	100-400mg qd
Dofetilide (Tikosyn®)	0.25mg-0.5mg q12h

VIII. Effectiveness

Findings from the CAST study warn of arrhythmogenic potential of class I antiarrhythmic agents. The selection of certain antiarrhythmic agents (e.g., Class I) should be reserved for the suppression and prevention of documented life-threatening ventricular arrhythmias. The FDA recommends that these agents be initiated in an inpatient setting. In addition, to the CAST trial, other publications have warned against the routine use of several Class I anti-arrhythmics. [9,10]

Despite the CAST results, certain antiarrhythmics such as procainamide and quinidine have been shown to be effective in the treatment of several arrhythmias such as Wolff-Parkinson-White syndrome.[11]

Amiodarone

Ventricular Arrhythmias

Results of two multicenter, randomized, placebo-controlled trials in patients with ventricular arrhythmias (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT] and European Myocardial Infarct Amiodarone Trial [EMIAT]) revealed that therapy with oral amiodarone appeared to reduce arrhythmia, death, and cardiac arrest. Also, the ARREST trial revealed that amiodarone is effective in the treatment of ventricular fibrillation after cardiac arrest in out-of-hospital patients.[12]

Amiodarone has been classified as a IIb therapeutic intervention for all three ventricular arrhythmias (Ventricular tachycardia, non-QT prolonged polymorphic VT, Ventricular fibrillation/pulseless VT) as a safe and useful agent with fair to good evidence to support is use.[13]

Heart Failure or Left Ventricular Systolic Dysfunction

The CHF-STAT trial was a four-year multicenter, double-blind, placebo-controlled trial that evaluated the long-terms effects of amiodarone on morbidity and mortality in patients with CHF and AF.[14] One-hundred and three patients had both CHF and AF and were randomized to either placebo or amiodarone therapy. Patients treated with amiodarone had a significant potential to convert to sinus rhythm ($p<0.05$). Additionally, patients who converted NSR had a lower mortality rate than those randomized to amiodarone and who did not convert.

Atrial Fibrillation

A number of nonrandomized, uncontrolled trials have found amiodarone to be effective for maintaining normal sinus rhythm in patients with AF that is refractory to conventional agents. Two randomized, nonblind trials have found amiodarone's efficacy to be equal to or superior to that of class IA drugs. [15,16]

Dofetilide (Tikosyn®)

Dofetilide has proven its benefit in converting or maintaining normal sinus rhythm in patients with AF. However, safety concerns such as torsades de pointes require for prescribing physicians to undergo certification prior to ordering dofetilide. Falk et al, evaluated a single bolus dose of intravenous dofetilide for the termination of sustained AF versus placebo. Results showed that 12.5% of patients who received dofetilide were converted to normal sinus rhythm compared to 0% in the placebo group. Also, Slavik et al, reported that oral dofetilide had quicker conversion rates in AF patients when compared with oral amiodarone and propafenone.[8]

The European and Australian Multicenter Evaluative Research on Atrial Fibrillation Dofetilide Study (EMERALD) compared the effectiveness and safety of oral dofetilide versus sotalol and placebo in patients with atrial fibrillation or flutter. Successful cardioversion was recorded in all dosing arms of the dofetilide group (125mcg [6%], 250mcg [11%], and 500mcg [29%]) compared to 5% and 1% cardioversion in the sotalol and placebo groups, respectively.[17]

The DIAMOND trial also demonstrated dofetilide's effectiveness in the treatment of patients who experienced a myocardial infarction and subsequently developed left ventricular systolic dysfunction. The authors concluded that dofetilide should be considered as a reasonable option for treatment of arrhythmias in these patients.

IX. Conclusions

As a result of the CAST study, Class I antiarrhythmics should be reserved for special or unique situations and when other more effective and safer alternatives have been exhausted. With the exception of dofetilde (Tikosyn®), moricizine (Ethmozine®), and tocainide (Tonocard®), all other antiarrhythmics reviewed are available in a generic formulation. Amiodarone's complex pharmacokinetic properties have raised concerns in the past regarding

equivalency with a generic formulation. However, studies have shown that steady-state concentrations can be achieved with a change or initiation of either formulation.[18]

All brand products within the class reviewed are comparable to each other and to the generic products within the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand antiarrhythmic is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
Cardiotonics (Digoxin) *(*AHFS Class 240408)
March 24, 2004

I. Overview

Digoxin was initially obtained from the foxglove plant and later found to posses positive inotropic effects on the heart. The efficacy of digoxin in patients with heart failure and atrial fibrillation has been well established and widely accepted.[1] Digoxin is a potent and selective inhibitor of the active transport of Na^+ and K^+ across the cell membrane. Its narrow therapeutic concentration range makes dosing of digoxin extremely vital in order to limit incidences of toxicity.[2] This review encompasses all dosage forms and strengths. Table 1 includes those cardiotonic agents included in this review.

Table 1. Cardiotonic Products in this Review

Generic Name	Example Brand Name(s)	Dosage Form
Digoxin	Digitek, Lanoxin	Oral tablet*
	Lanoxicaps	Oral capsule
	Lanoxin	Oral liquid*
	Lanoxin	Injectable*

*Generic formulations available

II. Current Treatment Guidelines

HEART FAILURE

Practice guidelines recommend for digoxin to be considered for patients who have symptoms of heart failure (NYHA Class II-III) caused by left ventricular systolic dysfunction while receiving standard therapy (ACE Inhibitors and diuretics).[3] Other recommendations include dosing of digoxin as 0.125mg to 0.25mg daily. Evidence suggests that the major benefit in heart failure is probably from neurohormonal modulation. This usually occurs at lower doses than needed for digoxin's inotropic effects. [4]

ATRIAL FIBRILLATION

Digoxin should not be used acutely to control ventricular rates in patients with atrial fibrillation due to its delay in onset of action. Digoxin should be used as a second-line agent although it may be ineffective during periods of vagal withdrawal or sympathetic activation such as exercise or stress.[5]

In patients with left ventricular systolic dysfunction (congestive heart failure) who have paroxysmal atrial fibrillation, digoxin may help prevent atrial fibrillation, because paroxysms can occasionally cause a worsening of heart failure in which case, digoxin may be effective as a positive inotropic agent. [6]

III. Indications

HEART FAILURE

For the treatment of mild-to-moderate heart failure. Where possible, digoxin should be used with a diuretic and an ACE Inhibitor.

ATRIAL FIBRILLATION

For the control of ventricular response rate in patients with chronic atrial fibrillation.

IV. Pharmacokinetics[7]

Absorption:

Absorption is delayed by food.

Digoxin tablets: 60-80%
Digoxin capsules: 90-100%
Digoxin Elixir: 70-85%

- Onset of action for oral formulations is generally 1-2 hours
- Peak effect for oral: 2-8 hours

Distribution:

Following administration a 6-8 hour tissue distribution phase is observed.
Vd (Normal renal function): 6-7L/kg
Decreased Vd with; Hyperkalemia, concomitant quindine therapy, renal failure
Increased Vd with: Hypokalemia, Hyperthyroidism

Metabolism:

Not dependent on cytochrome P-450 system. Usually metabolized (16%) by hydrolysis.

Excretion:

- 50-70% excreted unchanged in the urine.
- Half-life: 38-48 hours (dependent upon age, renal, and cardiac function)

V. Drug Interactions[8]

Tables 2 and 3 include digoxin drug interactions that may either increase or decrease digoxin serum levels.

Table 2. Drugs That Increase Digoxin Serum Levels

Amiodarone	Macrolides (Clarithromycin, Erythromycin)
Benzodiazepines (Alprazolam, Diazepam)	Propafenone
Bepridil	Propantheline
Cyclosporine	Quinidine
Diphenoxylate	Quinine
Indomethacin	Spironolactone
Itraconazole	Tetracycline
	Verapamil

Table 3. Drugs That Decrease Digoxin Serum Levels

Aminoglycosides	Kaolin/pectin
Antacids (Al & Mg)	Metoclopramide
Antineoplastics	Neomycin
Colestipol	Penicillamine
Charcoal	Rifampin
Cholestyramine	St. John's Wort

Sulfasalazine

VI. Adverse Drug Events[7,8]

Table 4 includes reported adverse drug reactions to digoxin.

Table 4. Digoxin Adverse Reactions

Cardiovascular	**Heart block, asystole, atrial tachycardia, , ventricular tachycardia, PR prolongation, ST segment depression**
CNS	**Visual disturbances (blurred vision), headache (3.2%), weakness, dizziness (4.9%), apathy, confusion , mental disturbances (4.1%), anxiety, depression, delirium, hallucinations, fever**
Dermatologic	**Maculopapular rash (1.6%), erythematous, vesicular or bullous rash, urticaria, pruritus, laryngeal edema, alopecia, shedding of fingernails or toenails**
GI	**Nausea (3.2%), vomiting (1.6%), diarrhea (3.2%), abdominal pain**
Miscellaneous	**Gynecomastia, Thrombocytopenia**

VII. Dosing and Administration[8]

Adult Loading Dose

Tablets: 0.5-0.75mg single initial dose
Capsules: 0.4-0.6mg single initial dose
Injection: 0.4-0.6mg single IV dose

Adult Maintenance Dose

0.05-0.3mg/day. (renal impairment: reduce to 50-75% of dose)

VIII. Effectiveness

Clinical Use of Digoxin in Heart Failure

The PROVED (Prospective Randomized study of Ventricular failure and efficacy of Digoxin) and RADIANCE (Randomized Assessment of Digoxin on Inhibition of Angiotensin Converting Enzyme) trials examined the effects of withdrawal of digoxin in patients with stable mild to moderate heart failure (i.e., NYHA class II and III) and systolic ventricular dysfunction. Withdrawal of digoxin resulted in a significant worsening of heart-failure symptoms in patients who received placebo compared with patients who continued to receive active drug therapy.[9, 10]

In the DIG trial, 6,800 patients with NYHA class II or III symptoms of heart failure and EF<0.45 were randomized to digoxin or placebo in addition to standard therapy. There was no difference in mortality between the treatment groups. However, fewer patients in the digoxin group were hospitalized as a result of worsening of heart failure.[11]

Table 5 summarizes outcomes from digoxin studies.

Table 5. Clinical Evidence for Digoxin

Study	*Sample*	*Results*
Heart Failure		
PROVED[9]	n=88, 12 weeks, placebo vs. digoxin with standard therapy	• Better preservation of exercise capacity in digoxin group • Withdrawal of digoxin resulted in worsening of symptoms
RADIANCE[10]	n=88, 12 weeks, placebo vs. digoxin with standard therapy	• Better preservation of exercise capacity in digoxin group • Withdrawal of digoxin resulted in worsening of symptoms
DIG[11]	n=6,801, digoxin with standard therapy vs. placebo	• No difference in mortality, but less hospitalizations in the digoxin group
Atrial Fibrillation		
Roberts SA, et al[12]	n=115, digoxin in Afib/Aflut	• Digoxin was effective for controlling normal sinus rhythm
Falk RH, et al[13]	n=36, digoxin vs. placebo in converting A fib to NSR	• Digoxin did not show effectiveness in conversion of NSR
Roth A, et al[14]	n=12, digoxin plus diltiazem in A fib	• Digoxin is effective when combined with medium-dose or high-does diltiazem for chronic Afib

IX. Conclusions

Ample evidence supports the use of digoxin particularly in Class II and III heart failure. Considering minor differences with respective pharmacokinetic parameters, all digoxin products are equally effective. All brand products within the class reviewed are comparable to each other and to the generics in this class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand cardiotonic is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review
Nitrates/Nitrites *(*AHFS Class 241208)
March 24, 2004

I. Overview

The organic nitrates relax most smooth muscle, including that in the arteries and veins. These effects subsequently lead to a reduction of myocardial oxygen demand secondary to venodilation. Organic nitrates are converted intracellularly to nitric oxide. Frequent repeated or continuous exposure to organic nitrates leads to a decrease in its pharmacological effects. Tolerance to nitrates is a result of dosage and frequency of administration of the preparation. The development of tolerance limits the efficacy of all chronic nitrate therapies regardless of route. Nitrate-free interval dosing can limit the degree of tolerance produced from chronic nitrate therapy.[1] Table 1 lists the nitrate/nitrite products included in this review. This review encompasses all dosage forms and strengths.

Table 1. Nitrate/Nitrite Products in this Review

Generic Name*	Brand Name Example(s)
Nitroglycerin*	Nitrostat, Nitroglyn, Nitrolingual, Nitroguard, Tridel
Nitroglycerin transdermal*	Nitro-Dur, Nitrek, Transderm Nitro
Nitroglycerin ointment	Nitro-Bid, Nitrol
Isosorbide mononitrate*	Ismo, Imdur, Monoket
Isosorbide dinitrate*	Isordil, Dilatrate-SR, Sorbitrate, Isochron

*Products are generically available

II. Current Treatment Guidelines

CHRONIC STABLE ANGINA

Treatment goals for Chronic Stable Angina include: 1. To relieve acute symptoms of myocardial ischemia, 2. prevent symptoms of myocardial ischemia, and 3. prevent unstable angina, myocardial infarction, and death.[2] Nitrates are recommended for the treatment or relief of acute symptoms of myocardial ischemia as well as for the prevention of symptoms associated with myocardial ischemia.[3]

Short-acting nitrates (SL tablets and spray) are recommended agents for relief of acute symptoms of myocardial ischemia. Their primary mechanism is to decrease MVO2 through systemic venodilation, which results in a reduction of preload and ventricular wall stress. Nitrates also increase oxygen supply by dilating coronary arteries and relieving vasospasm. Nitrates can also be utilized to prevent effort-induced angina.

Long-acting nitrates (transdermal and oral) are also recommended for the prevention of symptoms associated with myocardial ischemia. Nitrates can also be added to therapy in cases when first-line agents are contraindicated or if symptoms persist. A nitrate free interval of 8-12 hours should be followed to minimize tolerance to nitrates.[2]

UNSTABLE ANGINA & NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Sublingual nitroglycerin is considered a first-line agent to relieve symptoms of acute ischemia. Intravenous nitroglycerin is used for ongoing or recurrent pain of myocardial ischemia despite SL nitroglycerin and Beta-Blockers. Contraindications to nitroglycerin therapy include systolic BP < 90 and sildenafil use within 24 hours.[4]

CONGESTIVE HEART FAILURE

Guidelines recommend the use of isosorbide dinitrates in combination with hydralizine in patients who are truly intolerant (i.e., angioedema, renal failure) to ACE Inhibitors. This combination is aimed at decreasing preload and afterload. Target doses from mortality trials were isosorbide dinitrate 40mg every 6 hours. Nitrate tolerance does not appear to be a problem in heart failure; thus, nitrate-free interval is not usually recommended in this setting.[5]

HYPERTENSION

JNC-6 guidelines recommend the use of IV nitroglycerin for the treatment in hypertensive crisis for immediate reduction of blood pressure in patients where such a reduction is considered an emergency (hypertensive emergency). Nitroglycerin is the ideal agent in the treatment of hypertensive emergencies in particular if the patient has coronary complications such as, acute coronary insufficiency, left ventricular failure and postoperative hypertension.[6]

COCAINE-INDUCED ACUTE CORONARY SYNDROME

The American Heart Association Advanced Cardiac Life Support (ACLS) Committee considers nitroglycerin as a first-line agent to manage drug-induced coronary syndrome when standard emergency cardiac care guidelines may not be optimal or appropriate.[7]

III. Indications and Availability[8]

Table 2 includes availability and respective indications for the nitrates/nitrites.

Table 2. Nitrate/Nitrite Availability and Indications

Generic Name	Brand Name Example(s)	Generic Available	FDA Approved Indications
Nitroglycerin	Nitrostat, Nitroglyn, Tridel Nitrolingual, Nitroguard	Yes[1]	• Acute relief of angina attacks • Prophylaxis of angina pectoris
Nitroglycerin transdermal	Nitro-Dur, Transderm-Nitro, Nitrek	Yes[2]	• Prophylaxis and treatment of angina • Not for acute attacks
Nitroglycerin Ointment	Nitro-Bid, Nitrol	Yes	• Prophylaxis and treatment of angina • Not for acute attacks.
Isosorbide Mononitrate	Ismo, Imdur, Monoket	Yes	• Prophylaxis and treatment of angina • Not for acute attacks
Isosorbide Dinitrate	Isordil, Dilatrate-SR, Sorbitrate, Isochron	Yes	• Prophylaxis and treatment of angina • Not for acute attacks.

[1] Generic not available for Nitrolingual spray or Nitroguard
[2] Generic not available for 0.3mg/hr and 0.8mg/hr patch strengths

IV. Pharmacokinetics and Dosing

Excluding isosorbide mononitrate, nitrates have short to very short half-lives due to their hepatic metabolism and associated considerable first-pass effect. Nitrates also have large volumes of distribution, high clearance rates, and large individual variations in plasma and blood concentrations. The route of administration generally affects nitrate concentrations. There are also numerous problems limiting reliable pharmacokinetic estimates for nitrates.[1]

Table 3 lists the pharmacokinetic parameters of different formulations and common doses.

Table 3. Nitrate/nitrite Pharmacokinetic Comparison

Nitrates	Dosage Form	Onset (minutes)	Duration	Usual Dose
Nitroglycerin	IV	1-2	3-5 min	5µg/min: increase in 5µg/min increments
	Sublingual	1-3	30-60 min	0.3-0.6mg prn
	Translingual Spray	2	30-60 min	0.4mg/spray prn
	Transmucosal tablet	1-2	3-5 hrs	1mg every 3-5 hours
	Oral, sustained release	20-45	3-8 hrs	2.5-9mg two to four times a day
	Ointment	30-60	2-12 hrs	1-2 in. to skin every 4-8 hours
	Transdermal	30-60	Up to 24 hrs	1 disc (2.5-15mg) for 12-24 hours daily
Isosorbide dinitrate	Sublingual	2-5	1-3 hrs	2.5-10mg every 2-3 hours
	Oral	20-40	4-6 hrs	5-40mg every 6 hours
	Oral, sustained release	Up to 4hrs	6-8 hrs	40-80mg every 8-12 hours
Isosorbide mononitrate	Oral	30-60	N/A	Tablet: 10-40mg BID Cap: 60-120mg QD

V. *Drug Interactions*

Table 4 includes clinically significant (i.e., Category 1 or 2) drug interactions for the nitrates.

Table 4. Nitrate Drug Interactions[8]

Drug	Description
Alcohol	Severe hypotension and cardiovascular collapse may occur
Dihydroergotamine	Increased ergot bioavailability with resulting increased blood pressure or antagonism effect of vasodilating properties of nitrates
Sildenafil, Vardenafil	Potentiates the hypotensive effects of nitrates

VI. Adverse Drug Events

Common side effects of organic nitrates are generally all secondary to actions on the cardiovascular system. Headache is the most common side effect and can be severe. It usually decreases over a few days if treatment is continued. Transient episodes of dizziness and weakness associated with postural hypotension may develop and can occasionally progress to loss of consciousness. In addition, all the nitrates can occasionally produce drug rash particularly with transdermal nitroglycerin.[8] Table 5 lists potential adverse drug events related to nitrate use.

Table 5. Nitrate Adverse Drug Events

Cardiovascular (1-10%)	**Tachycardia, palpitations, hypotension, syncope, rebound hypertension, arrhythmias, atrial fibrillation, postural hypotension**
CNS (>10%)	**Headache, restlessness, weakness, vertigo, dizziness, agitation, anxiety, confusion, insomnia, nervousness, nightmares**
Dermatologic (<1%)	**Drug rash, flushing, pruritus, erythematous, local burning, itching**
GI (<1%)	**Nausea, vomiting, diarrhea, dyspepsia, abdominal pain, tooth disorder**
GU (<1%)	**Dysuria, impotence, urinary frequency**
Musculoskeletal (<1%)	**Arthralgias**
Respiratory (<1%)	**Bronchitis, pneumonia, upper respiratory infection**
Miscellaneous (<1%)	**Muscle twitching, pallor, perspiration, cold sweat, hemolytic anemia, blurred vision, edema, malaise, neck stiffness, rigors, increased appetite**

VII. Effectiveness[3-5,9-14]

ACC/AHA Chronic Stable Angina Guidelines

Pharmacologic treatment to reduce symptoms and prevent myocardial infarction and death includes sublingual nitroglycerin or nitroglycerin spray for immediate relief of angina. Additionally, long-acting nitrates are recommended as initial treatment in patients who can not tolerate, have history of a therapeutic failure, or presence of contraindications to other initial therapies.

ACC/AHA Unstable Angina Guidelines

In the treatment of unstable angina and non-ST-segment elevation myocardial infarction, anti-ischemic therapy with sublingual nitroglycerin tablets or spray followed by intravenous nitroglycerin is a Class I recommendation.

Congestive Heart Failure

Guidelines recommend the use of isosorbide dinitrates in combination with hydralizine in patients who are truly intolerant (i.e., angioedema, renal failure) to ACE Inhibitors. This combination is aimed at decreasing preload and afterload. Target doses from mortality trials were isosorbide dinitrate 40mg every 6 hours. Nitrate tolerance does not appear to be a problem in heart failure; thus, nitrate-free interval is not usually recommended in this setting.[5]

Additionally, Table 6 summarizes study results of nitrates use in the treatment of stable and unstable angina and heart failure.

Table 6. Nitrate Comparative Studies for Stable and Unstable Angina and Heart Failure

Study	*Sample*	*Results*
Stable Angina		
Parker JO	n=214, ISMN 5,10,20mg BID arms plus placebo, Duration: 3 weeks	Fewer episodes of angina in the 20mg dose, without tolerance
Thadani U, et al	n=116, ISMN 20mg BID plus placebo	ISMN was well tolerated & improved exercise performance, no rebound inc. in anginal attacks
Chrysant SG, et al	n=313, ISMN ER 30,60,120,240mg qAM plus placebo	ISMN ER 120 & 240mg QD prolonged exercise time to development of moderate effort-induced angina 4-12 hours post dose with no tolerance
Demots H, et al	n=206, TD NTG intermittent plus placebo, Duration: 4 weeks	Intermittent TD NTG was well tolerated with absolute response
Unstable Angina		
Kaplan, et al	n=35, unresponsive to standard therapy, given IV-NTG 10mcg/min	IV-NTG appears effective for angina refractory to standard medications
Heart Failure		
VHEFT-1	n=642, ISDN + Hydralazine (n=186), Prazosin (n=183), placebo.	Combination of vasodilators had the most significant benefit in all cause mortality (p=0.046)

VIII. Conclusions

Overwhelming evidence supports nitrates' beneficial effects for the management of chronic stable angina and acute angina attacks. Since nitrates have the same pharmacological effects, they can be generally interchanged with appropriate dosing adjustment depending on desired onset and duration.

All brand products within this class reviewed are comparable to each other and to the generics in that class and offer no significant clinical advantage over other alternatives in general use.

IX. Recommendation

No brand nitrate/nitrite products are recommended for preferred status.

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